# TABLE OF CONTENTS

## ORIGINAL RESEARCH

**226 Hypertension and Cardiovascular Diseases among Electronic and Combustible Cigarette Users**  
Grace E. Falk, MS-3, Hayrettin Okut, Ph.D., Mohinder R. Vindhyal, M.D., M.Ed., Elizabeth Ablah, Ph.D., MPH

**231 Clinical Outcome of Different Postoperative Prophylactic Strategies on Symptomatic Venous Thromboembolism after Total Knee Arthroplasty**  
Seth M. Wardyn, M.D., Alexander C.M. Chong, MSAE, MSME, Bruce E. Piatt, M.D.

**237 Patient Controlled Analgesia and an Alternative Protocol: A Comparison of Outcomes After Thoracic and Lumbar Surgery**  
Will Donelson, MS-4, Joey Dean, MBA, CPHRM, CPPS, Elizabeth Ablah, Ph.D., MPH, Clara Whitaker, Gina M. Berg, Ph.D., MBA, Kyle McCormick, MS-4, Hayrettin Okut, Ph.D., Camden Whitaker, M.D.

**241 The Association of Metabolic-Associated Fatty Liver Disease with Clinical Outcomes of COVID-19: A Systematic Review and Meta-Analysis**  
Umar Hayat, M.D., Muhammad Zubair Ashfaq, M.D., Luke Johnson, M.D., Ryan Ford, M.D., Chelsea Wuthnow, M.D., Kevin Kadado, M.D., Katia El Jurdi, M.D., Hayrettin Okut, Ph.D., William Ransom Kilgore, M.D., Maha Assi, M.D., Ali A. Siddiqui, M.D.

**247 Comprehension Profile of Patient Education Materials in Endocrine Care**  
Som P. Singh, Fahad M. Qureshi, Kiera G. Borthwick, Sagar Singh, Shreya Menon, Brandon Barthel, M.D.

## CASE REPORT

**253 Bilateral Upper Lobe Collapse Secondary to Vaping**  
Nicholas Tuck, M.D., Karen Gicho, M.D., Thomas Moore, M.D., FACP, FIDSA

**255 Takotsubo Cardiomyopathy in a Vaccinated Patient with Severe COVID-19**  
Osman Rahimi, D.O., Neilmegh L. Varada, D.O., Chriselyn Palma, D.O., Omar S. Al-Taweel, M.D., Kachon Lei, M.D., Dalia Hawwass, M.D., Chowdhury Ahsan, M.D., Ph.D.

**257 Scleroderma as an Unknown Cause of Pericardial Effusion**  

## COMMENTARY

**259 Mobile Health Clinics as a Healthcare Delivery Model to Address Community Disparities**  
Som P. Singh, Farhan Baig, Shipra Singh, M.D.
Hypertension and Cardiovascular Diseases among Electronic and Combustible Cigarette Users
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ABSTRACT
Introduction. Combustible cigarette use is associated with an increased risk of several cardiovascular diseases; however, less is known about associations between these cardiovascular conditions and electronic cigarette use.

Methods. This study investigated relationships between electronic and/or combustible cigarette use and diagnoses of cardiovascular diseases using the National Health Interview Survey from 2014, 2016, 2017, and 2018.

Results. Compared to non-users, dual users of electronic and combustible cigarettes had increased likelihood of having prior diagnoses of hypertension (OR 1.660, 95% CI = 1.519-1.814), stroke (OR 2.396, 95% CI = 2.011-2.855), diabetes mellitus (OR 1.219, 95% CI = 1.108-1.341), coronary artery disease (OR 2.211, 95% CI = 1.837-2.660), and myocardial infarction (OR 3.839, 95% CI = 3.232-4.560). Exclusive use of electronic cigarettes was associated with an increased likelihood of having hypertension compared to non-users (OR 1.244, 95% CI = 1.048-1.477).

Conclusions. There were no differences in diagnoses of stroke, diabetes mellitus, coronary artery disease, or myocardial infarction among exclusive electronic cigarette users compared to non-users; however, these associations could change as young electronic cigarette users with hypertension age, indicating the need for continued research.

INTRODUCTION
Cardiovascular diseases (CVDs), including myocardial infarction (MI) and stroke, accounted for more than 600,000 deaths among U.S. adults in 2017.1 Many factors contribute to one’s risk for developing CVDs, including tobacco use, hypertension, hyperlipidemia, diabetes mellitus (DM), and body mass index (BMI).2,3 Controlling these modifiable risk factors decreases the development of CVDs and subsequent mortality. Although it has long been established that combustible cigarette use increases the risk of CVDs and some cardiovascular risk factors, such as hypertension,2-4 the advent of electronic cigarettes (e-cigarettes) has brought new concerns to preventing and managing CVDs.

E-cigarettes, first introduced in 2006,5 had an estimated 8.1 million U.S. adult users in 2018.6 E-cigarettes offer an alternative to traditional combustible tobacco for nicotine delivery.7 However, preliminary data indicated that e-cigarettes increased one’s risk for the development of CVDs. For example, when compared to non-users, dual users of combustible and e-cigarettes have been associated with higher odds of MI, stroke, and coronary artery disease (CAD) than combustible cigarette users.8,9 However, much is still unknown about e-cigarette use and cardiovascular risk, especially as the age of e-cigarette users has changed. Therefore, the purpose of this study was to investigate relationships between e-cigarette use, combustible cigarette use, and dual use of combustible and e-cigarettes and diagnoses of hypertension, stroke, CAD, DM, or MI.

METHODS
Study Population. Participants 18 years or older were included in this study if they completed the National Health Interview Survey (NHIS) tobacco use questionnaire in 2014, 2016, 2017, or 2018. Participants were categorized by their combustible and/or e-cigarette use based on their responses to the NHIS questions. Participants who did not complete all questions in a relevant section of the survey were excluded.

Measures. This study was conducted using the NHIS data from the years 2014, 2016, 2017, and 2018. These years were chosen due to similar coding of the e-cigarette use in the NHIS data. Administered in all 50 states by the U.S. Centers for Disease Control and Prevention as a household interview survey, the goal of the NHIS is to monitor a variety of diseases and health related concerns in the U.S., including tobacco use.10 Because the NHIS is a de-identified database, IRB approval was not needed.

Participants were stratified into one of six groups based on their self-reported current or former use of combustible and e-cigarettes. The groups included: 1) current e-cigarette users, 2) current combustible cigarette users, 3) former combustible cigarette users currently using e-cigarettes, 4) former combustible cigarette users not currently using e-cigarettes, 5) current users of both combustible and e-cigarettes (referred to as dual users), and 6) never users of combustible or e-cigarettes (referred to as non-users). Those who reported using e-cigarettes every day or some days were identified as current e-cigarette users. Those who reported they had never used an e-cigarette, even one time, were considered non-users of e-cigarettes. Those who reported they had smoked at least 100 cigarettes in their entire lives were identified as combustible cigarette users; those who reported they had not smoked at least 100 cigarettes in their entire lives were considered non-users of combustible cigarettes.

Combustible cigarette users were stratified into current and former users; those who reported using combustible cigarettes every day or some days were considered current users of combustible cigarettes, and those who reported that at all were considered former users of combustible cigarettes. Former combustible cigarette users were stratified further into current and non-e-cigarette users based on their answers to the e-cigarette user questions. Participants who were non-users of combustible and e-cigarettes served as the comparison group for analyses.

Participants were evaluated for the presence or absence of a variety of CVDs based on their survey responses. Participants were considered

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to have been diagnosed with hypertension, stroke, DM, CAD, or MI if they reported they had ever been told by a doctor or other health professional that they had hypertension (also called high blood pressure), stroke, diabetes or sugar diabetes (other than during pregnancy), CAD, or MI, respectively. Potential confounding variables included: sex, BMI, and age and these were controlled for in each analysis.

Statistical Analysis. Data were analyzed using SAS Version 9.4 (SAS Inst. Inc. Cary, NC). Since NHIS data are obtained through a complex, multistage sample design that involves stratification, clustering, and oversampling of specific population subgroups, survey procedures in SAS were used to handle problems such as oversampling, weighting, stratification, or clustering for the data from population-based representative surveys. Rao-Scott chi-square goodness-of-fit tests with Taylor series method to calculate the variance was used for the design-adjusted tests of independence, or no association, between the nominal and/or categorical variables. Generalized multiple linear logistic models applied to test the association between the outcome variables and smoking status (e-cigarette use and combustible cigarette use) after adjusting for confounding variables such as sex, BMI, and age. The maximum likelihood parameter estimates implemented for the multiple logistic regression with SURVEYLOGISTIC in SAS to incorporate complex survey sample designs, including designs with stratification, clustering, and unequal weighting. This procedure utilizes Taylor series linearization methods for NHIS variance estimation to avoid increasing the Type I error. Data were reported as frequencies, means, standard deviations, and other summary statistics. All statistical tests at \( p \leq 0.05 \) were considered significant.

RESULTS

A total of 121,884 people completed the NHIS survey in 2014, 2016, 2017, and 2018. Of the 84,553 respondents meeting the inclusion and exclusion criteria for this study, 31% (n = 26,190) were current e-cigarette users, 76% (n = 64,599) were current combustible cigarette users, 37% (n = 3,169) were former combustible cigarette users currently using e-cigarettes, 21.0% (n = 17,788) were former combustible cigarette users not currently using e-cigarettes, 7.8% (n = 6,581) were dual users, and 56.7% (n = 47,937) were non-users.

Dual users were 1.660 times more likely (95% CI = 1.519-1.814) than non-users to have been diagnosed with hypertension. Compared to non-users, combustible cigarette users were 1.384 (95% CI = 1.277-1.499) times more likely, and e-cigarette users were 1.244 (95% CI = 1.048-1.477) times more likely to have been diagnosed with hypertension. Former combustible cigarette users currently using e-cigarettes were 1.308 (95% CI = 1.162-1.472) times more likely, and former combustible cigarette users not using e-cigarettes were 1.139 (95% CI = 1.082-1.198) times more likely to have been diagnosed with hypertension compared to non-users. Males were 1.252 (95% CI = 1.196-1.309) times more likely to have been diagnosed with hypertension than females. Increasing BMI by one kilogram/meter squared (kg/m²) was associated with 1.103 (95% CI = 1.098-1.107) times the odds and increasing age by one year was associated with 1.070 (95% CI = 1.068-1.072) times increased odds of hypertension diagnosis (Table 1).

Dual users were 2.396 (95% CI = 2.011-2.855) times more likely to have had a stroke compared to non-users. Current combustible cigarette users were 2.114 (95% CI = 1.815-2.463) times more likely to have had a stroke than non-users. There was no difference in stroke occurrence among e-cigarette users compared to non-users; however, former combustible cigarette users currently using e-cigarettes were 1.652 (95% CI = 1.245-2.191) times more likely to have had a stroke compared to non-users. Males were 1.114 (95% CI = 1.104-1.124) times more likely to have had a stroke than females. Increasing BMI by one kg/m² was associated with 1.032 (95% CI = 1.024-1.040) times increased likelihood, and increased age by one year was associated with 1.067 (95% CI = 1.063-1.070) times increased likelihood of a prior stroke (Table 1).

Compared to non-users, dual users were 1.219 (95% CI = 1.108-1.341) times more likely, and combustible tobacco users were 1.141 (95% CI = 1.023-1.274) times more likely to have been diagnosed with DM. There was no difference between non-users and e-cigarette users or former combustible cigarette users using e-cigarettes regarding likelihood of having been diagnosed with DM. Former combustible cigarette users not using e-cigarettes were 1.083 (95% CI = 1.010-1.162) times more likely to have been diagnosed with DM compared to non-users. Males were 1.124 times more likely to have been diagnosed with DM than females (95% CI = 1.067-1.183). Increased BMI and increased age also increased the likelihood of DM diagnosis (Table 1).

Compared to non-users, dual users were 2.211 (95% CI = 1.837-2.660) times more likely, and combustible cigarette users were 1.962 (95% CI = 1.611-2.151) times more likely to have been diagnosed with CAD. There was no difference in CAD occurrence between e-cigarette users and non-users. Compared to non-users, former combustible cigarette users currently using e-cigarettes were 2.278 (95% CI = 1.791-2.898) times more likely, and former combustible cigarette users not using e-cigarettes were 1.531 (95% CI = 1.402-1.672) times more likely to have been diagnosed with CAD. Males were 1.973 (95% CI = 1.817-2.143) times more likely to have been diagnosed with CAD than females. Increasing BMI by one kg/m² was associated with 1.047 (95% CI = 1.040-1.054) times increased likelihood and increasing age by one year was associated with 1.086 (95% CI = 1.082-1.090) times increased likelihood of CAD diagnosis (Table 1).

Dual users were 3.839 (95% CI = 3.232-4.560) times more likely to have had a MI compared to non-users. Combustible cigarette users were 2.836 (95% CI = 2.442-3.294) times more likely to have had a MI compared to non-users. There was no difference in likelihood of MI occurrence between non-users and e-cigarette users. Compared to non-users, former combustible cigarette users currently using e-cigarettes were 2.448 (95% CI = 1.880-3.189) times more likely, and former combustible cigarette users not currently using e-cigarettes were 1.752 (95% CI = 1.576-1.947) times more likely to have had a MI. Males were 2.142 (95% CI = 1.946-2.359) times more likely to have had a MI compared to females. Increasing BMI by one kg/m² was associated with 1.041 (95% CI = 1.034-1.048) times increased likelihood and increasing age by one year was associated with 1.077 (95% CI = 1.073-1.081) times increased likelihood of a prior MI (Table 1).
Table I. Condition among e-cigarette and/or combustible cigarette users compared to non-users.

<table>
<thead>
<tr>
<th>Group</th>
<th>Hypertension Odds Ratio (95% CI)</th>
<th>Stroke Odds Ratio (95% CI)</th>
<th>Diabetes Mellitus Odds Ratio (95% CI)</th>
<th>Coronary Artery Disease Odds Ratio (95% CI)</th>
<th>Myocardial Infarction Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-Cigarette Only Users</td>
<td>1.244 (1.048-1.477)*</td>
<td>1.058 (0.586-1.911)</td>
<td>1.108 (0.972-1.263)</td>
<td>0.856 (0.519-1.412)</td>
<td>0.984 (0.555-1.747)</td>
</tr>
<tr>
<td>Combustible Cigarette Only Users</td>
<td>1.384 (1.277-1.499)*</td>
<td>2.114 (1.815-2.463)*</td>
<td>1.141 (1.023-1.274)*</td>
<td>1.862 (1.611-2.151)*</td>
<td>2.838 (2.442-3.294)*</td>
</tr>
<tr>
<td>Former Combustible Cigarette Users Currently Using E-Cigarettes</td>
<td>1.308 (1.162-1.472)*</td>
<td>1.652 (1.245-2.191)*</td>
<td>0.952 (0.831-1.091)</td>
<td>2.278 (1.791-2.898)*</td>
<td>2.448 (1.880-3.189)*</td>
</tr>
<tr>
<td>Former Combustible Cigarette Users Not Currently Using E-Cigarettes</td>
<td>1.139 (1.082-1.198)*</td>
<td>1.287 (1.151-1.436)*</td>
<td>1.083 (1.010-1.162)*</td>
<td>1.531 (1.402-1.672)*</td>
<td>1.752 (1.576-1.947)*</td>
</tr>
<tr>
<td>Dual Users of E-Cigarettes and Combustible Cigarettes</td>
<td>1.660 (1.519-1.814)*</td>
<td>2.396 (2.011-2.855)*</td>
<td>1.219 (1.108-1.341)*</td>
<td>2.211 (1.837-2.660)*</td>
<td>3.839 (3.232-4.560)*</td>
</tr>
<tr>
<td>Sex (males compared to females)</td>
<td>1.252 (1.196-1.309)*</td>
<td>1.114 (1.014-1.224)*</td>
<td>1.124 (1.067-1.183)*</td>
<td>1.973 (1.817-2.143)*</td>
<td>2.142 (1.946-2.359)*</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>1.103 (1.098-1.107)*</td>
<td>1.032 (1.024-1.040)*</td>
<td>1.056 (1.055-1.183)*</td>
<td>1.047 (1.040-1.054)*</td>
<td>1.041 (1.034-1.048)*</td>
</tr>
<tr>
<td>Age</td>
<td>1.070 (1.068-1.072)*</td>
<td>1.067 (1.063-1.070)*</td>
<td>1.030 (1.029-1.032)*</td>
<td>1.086 (1.082-1.090)*</td>
<td>1.077 (1.073-1.081)*</td>
</tr>
</tbody>
</table>

*Indicates significant difference.

**DISCUSSION**

The current study suggested that e-cigarette use, whether alone or combined with concurrent combustible cigarette use, increased the likelihood of a person being diagnosed with hypertension. Several small studies have evaluated the short-term effects of e-cigarette use on blood pressure with mixed findings; however, this was the first large-scale study to analyze the prevalence of hypertension among e-cigarette users compared to non-users. Despite these previous findings, the current study found that e-cigarette users were more likely to have hypertension than non-users. However, the results of the current study change as e-cigarette users age.

Regarding the occurrence among e-cigarette users is needed to observe if the findings could go on to experience a greater frequency of strokes than non-users. Continued monitoring of stroke occurrence among e-cigarette users is needed to observe if the findings of the current study change as e-cigarette users age. In addition to hypertension, DM was another stroke risk factor. Therefore, the currently young population of e-cigarette users who have never smoked combustible cigarettes were younger than 35 years. Most combustible cigarette users, on the other hand, were 45 to 64 years. Because stroke risk was greater among older individuals, it was possible that the younger age of e-cigarette users tended to be younger than 35 years. Therefore, the currently young population of e-cigarette users who have never smoked combustible cigarettes were younger than 35 years. Most combustible cigarette users, on the other hand, were 45 to 64 years. Because stroke risk was greater among older individuals, it was possible that the younger age of e-cigarette users in the current analysis was protective against stroke. Additionally, older individuals were more likely to have been diagnosed with conditions that are predisposed to stroke, like hypertension, and an increased duration of uncontrolled hypertension increases one’s risk for having a stroke. Therefore, the currently young population of e-cigarette users who were more likely to have hypertension than non-users based on the current analysis, could go on to experience a greater frequency of strokes than non-users. Continued monitoring of stroke occurrence among e-cigarette users is needed to observe if the findings of the current study change as e-cigarette users age.

Taylor et al. may have used a different sampling method or different criteria for defining stroke, CAD, and MI. The current analysis was the first large study to analyze associations between e-cigarette use and DM while adding analyses of DM among current and former combustible cigarette users. Compared to non-users in the current analysis, dual users, combustible cigarette users, and former combustible cigarette users not currently using e-cigarettes, a sympathetic nervous system stimulant, and a component of combustible cigarettes, it is difficult to pinpoint a common underlying component in both combustible and e-cigarettes that could be contributing to the increased occurrence of hypertension among combustible and e-cigarette users in the current study. However, because most e-cigarettes contain nicotine, a sympathetic nervous system stimulant, and a component of combustible cigarettes, the results of the current study suggested that the consumption of nicotine in any form, including e-cigarettes, increases the chance of a person developing hypertension. Regardless of exactly which ingredient(s) of combustible and e-cigarettes contribute to the increased occurrence of hypertension observed among users in the current analysis, these results indicated a need for public health action, as hypertension is a major risk factor for stroke, CAD, and MI.
e-cigarettes were more likely to have been diagnosed with DM. However, when compared to non-users, there was no difference in association between having a prior diagnosis of DM and e-cigarette use, nor former combustible cigarette use with current e-cigarette use. The lack of association between former combustible cigarette users currently using e-cigarettes and DM diagnosis was unique from the trends observed for the other CVDs analyzed in the current study, where a lack of association generally occurred among e-cigarette users when compared to non-users. This could be due to potential differences in weight gain after cessation of combustible cigarettes, as individuals who stop using combustible cigarettes were most likely to experience weight gain and be diagnosed with DM within seven years of cessation. If, in fact, the cessation of nicotine, generally present in both combustible and e-cigarettes, was associated with weight gain and increased risk of DM development, then use of e-cigarettes among former combustible cigarette users potentially could explain these study findings. More research is needed to understand the associations between DM occurrence, combustible cigarette cessation, and e-cigarette use.

DM is a risk factor for CAD, and the current analysis investigated associations between diagnoses of CAD and combustible and e-cigarette use. Compared to non-users, dual users and former combustible cigarette users currently using e-cigarettes were twice as likely to have been diagnosed with CAD. Although there were increased odds of CAD among current combustible cigarette users and former combustible cigarette users not using e-cigarettes compared to non-users, there was no difference in the likelihood of CAD among e-cigarette users compared to non-users. These findings supported previous research. However, the current study was unique from previous research in its separate evaluation of CAD and its control group that included respondents who never used combustible or e-cigarettes. Similar to stroke, the lack of association between CAD and e-cigarette use in the current analysis could be related to age differences between combustible and e-cigarette users. CAD was most prevalent among older adults, affecting 19.8% of adults older than 65 years compared to 1.2% of adults 18 to 44 years; however, most e-cigarette users were younger than 35 years. Thus, as e-cigarette users age and as hypertension, a risk factor for CAD, progresses in this group, it is possible that the occurrence of CAD among e-cigarette users will change. Because CAD was a risk factor for MI, continued monitoring for the development of CAD among e-cigarette users is warranted.

MI occurrence has been analyzed previously among e-cigarette users, and the current analysis built upon these findings from 2014 and 2016. In the current analysis, compared to non-users, dual users were 3.839 times more likely to have had a MI, while former combustible cigarette users using e-cigarettes were 2.448 times more likely to have had a MI, which was slightly lower than the 4.62 times increased odds of MI calculated among dual users in the current analysis. When compared to non-users, dual users were 3.839 times more likely to have had a MI, which was slightly lower than the 4.62 times increased odds of MI calculated among dual users in the previous study.

For stroke, the current analysis suggested that, compared to non-users, dual users and former combustible cigarette users currently using e-cigarettes were 1.752 times more likely to have experienced a stroke. This was consistent with previous estimates that, when compared to non-users, the odds of MI were greater among former combustible cigarette users currently using e-cigarettes than among former combustible cigarette users not using e-cigarettes. Unlike previous research, the current analysis did not identify an association between exclusive e-cigarette consumption and likelihood of experiencing a MI compared to non-users. This could be due to differences in how analyses were conducted, as the previous study stratified e-cigarette users by daily and non-daily consumption in an adjusted model. Additionally, these findings could be due to changes in e-cigarette consumption trends in the U.S. in 2017 and 2018. E-cigarette use increased 2.4% among adults 18 to 24 years in the U.S. from 2017 to 2018, while e-cigarette use among adults 45 or older decreased. Thus, because e-cigarette users tend to over-represent younger generations, who are less likely to experience a MI based on age alone, it was possible that the differences observed between the current analysis and the former study could reflect these changing trends in e-cigarette use. More research is needed to understand the effects of exclusive e-cigarette use on cardiovascular health better, including MI.

Limitations. The results of this study relied on survey responses, which were affected by recall and non-response biases. Additionally, e-cigarettes have been available commercially in the U.S. for 15 years, limiting the time for long-term observation on the association of e-cigarette use and chronic health conditions. However, the limited knowledge of the long-term effects of e-cigarettes on CVDs validated the need for the current and future analyses.

CONCLUSIONS

The analyses of each cardiovascular condition in the current study suggested that, compared to non-users, dual users of combustible and e-cigarettes had the greatest likelihood of reporting having been diagnosed with hypertension, stroke, DM, CAD, and MI. The current analysis extended previous research findings regarding associations between e-cigarette use and these CVDs. The increased occurrence of hypertension observed among all forms of e-cigarette use was concerning for future development of CVDs among the generally young population of e-cigarette users. The findings of this study indicated that e-cigarettes were not a cardiovascular risk-free alternative to combustible cigarettes.

REFERENCES

E-CIGS, HTN, AND CVD
continued.


Clinical Outcome of Different Post-operative Prophylactic Strategies on Symptomatic Venous Thromboembolism after Total Knee Arthroplasty

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ABSTRACT

INTRODUCTION

The objective of this study was to evaluate the use of different post-operative prophylactic strategies on the rates of symptomatic venous thromboembolic events (VTE) incidence after primary total knee arthroplasty (TKA).

METHODS

A retrospective study of patients who underwent primary TKA procedure was performed from January 2015 through July 2020. Outcomes examined prophylaxis medication used during inpatient and outpatient care, amount of medication, length of medication, complications occurring within 90 days post-operatively, including symptomatic VTE (deep venous thrombosis (DVT), and pulmonary embolism (PE)), gastrointestinal (GI) bleeding requiring medical attention, change in management protocols after post-operative complications, and mortality.

RESULTS

In total, 5,663 cases were included (mean age 66 ± 10 years, mean BMI 34.1 ± 7.1 kg/m²). The overall post-operative complication rate was 0.9% (DVT: 0.5%, PE: 0.3%, VTE: 0.04%, and GI bleeding: 0.09%). Enoxaparin use as inpatient anticoagulation medication was reduced significantly (67% vs. 13%, p < 0.001), and apixaban was increased significantly (6% vs. 49%, p < 0.001). Average hospital stays were reduced significantly among the years (3 ± 2 days vs. 2 ± 1 days, p < 0.001), and complication rates were not significantly different between the five years (-1%, p < 0.001). Most post-operative complications occurred on either aspirin 325 mg (36%) or apixaban (26%). However, the relative risk ratio results indicating that utilization of warfarin, rivaroxaban, and coumadin are the most common methods of DVT chemoprophylaxis used by orthopedists.3,5,10,12-16 Despite decades of clinical experience, new technology on implant design, better surgical procedure, improved physical therapy protocol, and hundreds of studies, the ideal method of VTE prophylaxis remains controversial. This has resulted in variability and inconsistency of prophylaxis for TKA patients and a concern that many patients may be left at risk with no prophylaxis or suboptimal prophylaxis. The specific aim of this study was to evaluate the use of different post-operative prophylactic strategies on the rates of symptomatic VTE incidence after primary TKA.

METHODS

Subjects. Institutional Review Board approval was obtained for this study. This retrospective study reviewed the clinical charts of patients (greater than 18 years of age) who had undergone primary TKA procedures from January 2015 through July 2020 from hospitals within a single institution in the Midwest region. Patients who underwent unicompartmental knee arthroplasty, revision knee arthroplasty, same day bilateral TKAs, or had less than 90 days follow-up without any complication were excluded from this study.

Variables. The retrospective chart review gathered patient demographic data including age, gender, body mass index (BMI), surgical date, site of procedure, prophylaxis medication used during inpatient care and outpatient care, amount of medication, length of medication, and length of hospital stay. Post-operative complications included those occurring within 90 days post-operatively including symptomatic VTEs and upper and lower gastrointestinal (GI) bleeding requiring medical attention. Change in management protocols after post-operative complications and mortality also were recorded.

Statistical Analysis. Descriptive statistics of the mean, standard
RESULTS

There were 6,440 primary TKA cases identified, with only 5,663 of those cases (2,254 males and 3,409 females) included in this study due to exclusion criteria or incomplete inpatient medication. The mean age was 66 ± 10 years (range: 23 - 96 years) and the mean BMI was 34.1 ± 7.1 kg/m² (range: 17.7 - 79.1 kg/m²). The mean hospital stay was 2.1 ± 1.3 days (range: 0 - 34; Table 1). There were 155 patient deaths recorded in this study, and 10% (n = 15) were within 90 days post-operatively due to natural causes or other medical conditions.

There were 0.9% (n = 50) post-operative complications including symptomatic DVT (0.5%), PE (0.3%), unspecified VTE (0.04%), and upper and lower GI bleeding (0.09%). The mean age for these symptomatic DVT (0.5%), PE (0.3%), unspecified VTE (0.04%), and upper and lower GI bleeding (0.09%). The mean age for these complication groups was 65 ± 11 years (range: 41 - 83 years) and the mean BMI was 33.6 ± 6.0 kg/m² (range: 22.4 - 50.0 kg/m²). The mean hospital stay for all complication groups was 3.1 ± 2.6 days (range: 1 - 12; Table 1).

There were seven different anticoagulants prescribed as inpatient medication in this study: enoxaparin, rivaroxaban, warfarin, apixaban, aspirin 325 mg, aspirin 81 mg, and heparin (Table 2). Enoxaparin (34% of the patients) was the most frequently used medication for inpatient anticoagulation for DVT chemoprophylaxis. Utilization of rivaroxaban, aspirin 325 mg, aspirin 81 mg, and heparin as inpatient anticoagulation medication were more likely to increase the risk of symptomatic VTE incidence compared to other anticoagulants.

When comparing the yearly breakdown, utilization of enoxaparin as inpatient anticoagulation medication was reduced significantly over the five years (67% vs. 13%, p < 0.001), except the years 2018 and 2019 (p = 0.61). The other inpatient anticoagulation medications were increased significantly over the years, especially apixaban (6% vs. 49%, p < 0.001; Figure 1). Average hospital stays were reduced significantly among the years (2.8 ± 1.7 days vs. 1.5 ± 1.0 days, p < 0.001), except the years 2018 and 2019 (p = 0.61). The complication rates were not significantly different across the five years (-1%), except the years 2016 and 2019 (0.4% vs. 1.2%, p = 0.04; Table 3).

The three most common outpatient anticoagulation medications prescribed were apixaban (31%), aspirin 325 mg (38%), and enoxaparin (14%). Of the post-op complications, the most common outpatient medications used were apixaban (26%) and aspirin 325 mg (36%). However, the relative risk ratio results indicating that utilization of warfarin, rivaroxaban, and aspirin 81 mg as outpatient anticoagulation medication were more likely to increase the risk of symptomatic VTE incidence compared to other anticoagulants. The average time of complication detection was 208 ± 21.1 days (range: 1 - 87 days), and 40% of the complications found occurred after the patient had completed their anticoagulation medication (Table 4).

When comparing the time of complication and length of time on outpatient anticoagulation medication, the results of this study demonstrated that when enoxaparin, rivaroxaban, and apixaban were used as outpatient anticoagulation medications, more than 54% of complication events occurred after the patient had completed their medication (Table 5).

Table 1. Patient demographics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (N = 5,663)</th>
<th>Complication (N = 50)</th>
<th>DVT (N = 28)</th>
<th>PE (N = 15)</th>
<th>VTE (N = 2)</th>
<th>GI Bleed (N = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3,409 (60%)</td>
<td>30 (60%)</td>
<td>14 (50%)</td>
<td>12 (80%)</td>
<td>2 (100%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Male</td>
<td>2,254 (40%)</td>
<td>20 (40%)</td>
<td>14 (50%)</td>
<td>3 (20%)</td>
<td>-</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Age, mean years ± SD (range)</td>
<td>66 ± 10 (23 - 96)</td>
<td>65 ± 11 (41 - 83)</td>
<td>65 ± 12 (41 - 82)</td>
<td>63 ± 10 (47 - 77)</td>
<td>70 ± 4 (67 - 72)</td>
<td>73 ± 11 (56 - 83)</td>
</tr>
<tr>
<td>BMI, mean kg/m² ± SD (range)</td>
<td>34.1 ± 7.1 (17.7 - 79.1)</td>
<td>33.6 ± 6.0 (22.4 - 50.0)</td>
<td>32.2 ± 5.1 (22.4 - 49.0)</td>
<td>35.5 ± 6.1 (23.8 - 43.9)</td>
<td>41.0 ± 12.6 (32.1 - 50.0)</td>
<td>32.9 ± 5.7 (26.8 - 40.3)</td>
</tr>
<tr>
<td>Site of Procedure, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>2,743 (48%)</td>
<td>25 (50%)</td>
<td>15 (54%)</td>
<td>8 (53%)</td>
<td>-</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Right</td>
<td>2,920 (52%)</td>
<td>25 (50%)</td>
<td>13 (46%)</td>
<td>7 (47%)</td>
<td>2 (100%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Hospital stay, mean days ± SD (range)</td>
<td>2.1 ± 1.3 (0 - 34)</td>
<td>3.1 ± 2.6 (1 - 12)</td>
<td>2.3 ± 1.7 (1 - 9)</td>
<td>4.7 ± 3.7 (1 - 12)</td>
<td>2.5 ± 0.7 (2 - 3)</td>
<td>2.8 ± 1.1 (1 - 4)</td>
</tr>
</tbody>
</table>
Table 2. Inpatient medication effects on complications.

<table>
<thead>
<tr>
<th>Inpatient Medication</th>
<th>Overall (N = 5,663)</th>
<th>Complication (n = 50)</th>
<th>Relative Risk Ratio (RR)</th>
<th>95% RR Confidence Interval</th>
<th>DVT (n = 28)</th>
<th>PE (n = 15)</th>
<th>VTE (n = 2)</th>
<th>GI Bleed (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>1,941 (34%)</td>
<td>16 (32%)</td>
<td>0.9</td>
<td>(0.6 - 1.6)</td>
<td>9 (32%)</td>
<td>4 (27%)</td>
<td>1 (50%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>484 (9%)</td>
<td>6 (12%)</td>
<td>1.5</td>
<td>(0.4 - 3.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Warfarin</td>
<td>182 (3%)</td>
<td>1 (2%)</td>
<td>0.6</td>
<td>(0.1 - 4.4)</td>
<td>-</td>
<td>1 (7%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1,785 (32%)</td>
<td>10 (20%)</td>
<td>0.5</td>
<td>(0.5 - 1.1)</td>
<td>2 (7%)</td>
<td>4 (27%)</td>
<td>1 (50%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Aspirin (325 mg)</td>
<td>1,140 (20%)</td>
<td>13 (26%)</td>
<td>1.4</td>
<td>(0.5 - 2.6)</td>
<td>9 (32%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aspirin (81 mg)</td>
<td>122 (2%)</td>
<td>2 (4%)</td>
<td>1.9</td>
<td>(0.3 - 7.7)</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heparin</td>
<td>9 (0.2%)</td>
<td>2 (4%)</td>
<td>26.2</td>
<td>(0.3 - 91.8)</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3. Yearly comparison of complication to hospital stay time and complication rate.

<table>
<thead>
<tr>
<th>Year</th>
<th>Hospital stay (days)</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>2.8 ± 1.7 (1 - 34)</td>
<td>10 (1.0%)</td>
</tr>
<tr>
<td>2016</td>
<td>2.6 ± 1.2 (1 - 20)</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>2017</td>
<td>2.2 ± 1.0 (0 - 10)</td>
<td>8 (0.7%)</td>
</tr>
<tr>
<td>2018</td>
<td>1.5 ± 1.1 (0 - 14)</td>
<td>11 (0.9%)</td>
</tr>
<tr>
<td>2019</td>
<td>1.5 ± 1.0 (0 - 9)</td>
<td>12 (1.2%)</td>
</tr>
</tbody>
</table>

Note: Year 2020 was excluded due to only have four months of data.
Table 4. Outpatient medication effects on complications.

<table>
<thead>
<tr>
<th>Outpatient Medication</th>
<th>Overall (N = 5,663)</th>
<th>Complication (n = 50)</th>
<th>Relative Risk Ratio</th>
<th>95% RR Confidence Interval</th>
<th>DVT (n = 28)</th>
<th>PE (n = 14)</th>
<th>VTE (n = 2)</th>
<th>GI Bleed (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>800 (14%)</td>
<td>7 (14%)</td>
<td>1.0</td>
<td>(0.5 - 2.2)</td>
<td>3 (11%)</td>
<td>1 (7%)</td>
<td>1 (50%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>266 (5%)</td>
<td>3 (6%)</td>
<td>1.3</td>
<td>(0.3 - 4.1)</td>
<td>3 (11%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Warfarin</td>
<td>284 (5%)</td>
<td>5 (10%)</td>
<td>2.1</td>
<td>(0.4 - 5.3)</td>
<td>1 (4%)</td>
<td>4 (27%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Apixaban (325 mg)</td>
<td>1,766 (31%)</td>
<td>13 (26%)</td>
<td>0.8</td>
<td>(0.5 - 1.5)</td>
<td>5 (18%)</td>
<td>5 (33%)</td>
<td>1 (50%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Warfarin (81 mg)</td>
<td>295 (5%)</td>
<td>4 (8%)</td>
<td>1.6</td>
<td>(0.4 - 4.4)</td>
<td>2 (7%)</td>
<td>2 (13%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to Complication</th>
<th>Overall (N = 5,663)</th>
<th>Complication (n = 50)</th>
<th>Relative Risk Ratio</th>
<th>95% RR Confidence Interval</th>
<th>DVT (n = 28)</th>
<th>PE (n = 14)</th>
<th>VTE (n = 2)</th>
<th>GI Bleed (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On</td>
<td>-</td>
<td>30 (60%)</td>
<td>-</td>
<td>-</td>
<td>17 (61%)</td>
<td>1 (7%)</td>
<td>2 (40%)</td>
<td>-</td>
</tr>
<tr>
<td>Off</td>
<td>-</td>
<td>20 (40%)</td>
<td>-</td>
<td>-</td>
<td>11 (39%)</td>
<td>4 (27%)</td>
<td>2 (100%)</td>
<td>3 (60%)</td>
</tr>
</tbody>
</table>

Table 5. Outpatient medication regimen on complications.

<table>
<thead>
<tr>
<th>Overall complication (N = 50)</th>
<th>Time on Outpatient Medication (Days)</th>
<th>Time of Complication (Days)</th>
<th>On Regimen</th>
<th>Off Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin (n = 7)</td>
<td>8.4 ± 1.7 (7 - 12)</td>
<td>16.0 ± 15.8 (1 - 40)</td>
<td>3 (43%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Rivaroxaban (n = 3)</td>
<td>11.0 ± 2.7 (9 - 14)</td>
<td>39.3 ± 19.7 (26 - 62)</td>
<td>-</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Warfarin (n = 5)</td>
<td>50.0 ± 45.8 (0 - 90)</td>
<td>8.6 ± 7.8 (2 - 22)</td>
<td>4 (80%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Apixaban (325 mg) (n = 13)</td>
<td>19.1 ± 17.0 (9 - 60)</td>
<td>25.9 ± 23.2 (2 - 75)</td>
<td>6 (46%)</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>Aspirin (81 mg) (n = 4)</td>
<td>26.2 ± 7.6 (6 - 32)</td>
<td>22.1 ± 24.2 (2 - 87)</td>
<td>13 (72%)</td>
<td>5 (28%)</td>
</tr>
</tbody>
</table>

DISCUSSION

The specific aim of this study was to evaluate the use of different post-operative prophylactic strategies on the rates of symptomatic VTE incidence after primary TKA. Complication rates were not significantly different across the five years despite which inpatient or outpatient anticoagulation prophylaxis was used. Forty percent of the complications took place after patient had completed their anticoagulation medication, and when looking specifically at enoxaparin, rivaroxaban, and apixaban as outpatient prophylaxis, more than 54% of complications occurred after the patient had completed their medication.

Patients undergoing TKA are at high risk of VTE if they do not receive anticoagulation as it is considered as the third most frequent cause for hospital readmission after TKA. There is considerable debate regarding the appropriate post-operative prophylactic agent for patients undergoing primary TKA, with many surgeons making decisions based on anecdotal evidence and historical precedent. As VTE is an uncommon event with reported rates of symptomatic VTEs within 90 days of TKA at less than 2% and the mortality rates from VTE following lower limb arthroplasty low (less than 1%), it is difficult to acquire sufficient statistical power to discern differences between agents.

Over the five-year study period, there was a transition from using enoxaparin to oral anticoagulation therapy such as apixaban, rivaroxaban, and aspirin. At the end of the study period, some surgeons’ preference was to prescribe all their patients one of the direct oral inhibitors (e.g., apixaban, rivaroxaban), whereas others were risk stratifying based on patients’ history. Due to this study being a retrospective review, there was no standardization of medication or length of time. Patients that were on anticoagulation before the procedure also were restarted on their previous regimen after surgery.

Two previous meta-analyses found that low-dose aspirin has a similar efficacy in the prevention of VTE when compared to enoxaparin. Recently, there has been more literature comparing low dose aspirin to high-dose aspirin. In a study by Faour et al., low-dose aspirin was found to be as efficacious to high-dose aspirin in the prevention of VTE following TKA. In another study by Parvizi et al., the efficacy and adverse event profiles of low-dose (81 mg twice daily) versus high-dose aspirin (325 mg twice daily) regimens were examined.
high-dose aspirin (325 mg twice daily) regimens were examined for patients undergoing total hip and knee arthroplasty and they also found that low dose aspirin was as efficacious to high-dose aspirin in the prevention of VTE. A meta-analysis of randomized controlled trials comparing dabigatran, rivaroxaban, apixaban, and enoxaparin reported incidence of symptomatic VTE as 0.7%, 0.5%, 0.5%, and 0.8%, respectively. None of these studies mentioned compared prophylaxis regimens in patients with known hypercoagulable risk factors such as those with inherited blood clotting disorders, history of previous VTE, obesity, malignancy, estrogen therapy, and varicose veins and increased age.

One result of this study captured VTEs occurred at an average of 20 days after discharge, and 40% of those patients had completed their anticoagulation medication at the time of VTE complication. Specifically, the average length of apixaban, rivaroxaban, and enoxaparin dosing were 17, 10, and 8 days, respectively, while 54% of the apixaban, 100% of the rivaroxaban, and 57% of the enoxaparin post-op symptomatic VTEs occurred after medication completion. These findings were similar to a study by Warwick et al. in 2007, where they found that mean times to VTE after TKA was 9.7 days (SD 14.1 days), but 27% of patients who received the recommended forms of prophylaxis were no longer receiving it after 7 days. Current treatment guidelines for patients following TKA recommended the routine administration of a prophylactic anticoagulant for at least 10 days after the operation. The American Academy of Orthopaedic Surgeons (AAOS) and the American College of Clinical Pharmacy (ACCP) guidelines for VTE prophylaxis for patients undergoing elective TKA also stated the duration must be at least 10 to 14 days, and up to 35 days regardless of the medication being used. This indicated it was likely some complications could have been avoided by extending the duration of the medications.

One possibility for the average time to VTE to occur after average medication completion could be due to a rebound hypercoagulable effect. In 2018, Li et al. reported that although a rebound effect is controversial, physicians should be aware of the possibility. The mechanism behind this rebound hypercoagulable phenomenon after discontinuation is uncertain. It has been suggested for rivaroxaban that decreased plasma concentration after its discontinuation results in loss of prothrombinase/factor Xa inhibition at the thrombotic sites, thus leading to prothrombotic activity. Another possibility is the anticoagulation medications were masking the symptoms of the VTE or preventing it from enlarging. Often DVTs are created intraoperative, confirmed by venographic and leg-scanning studies, but are asymptomatic or silent until they can enlarge due to prolonged impairment of venous function, sustained hypercoagulability, or impairment of the endogenous anticoagulant systems.

Limitations. This study had certain limitations. First, a small sample size of post-operative complications found made applying tests of significance to certain variables difficult. A total of 3,400 patients would afford an adequate trial at 95% power and 5% significance, assuming a baseline symptomatic VTE event rate of 1%. Second, this study was a retrospective chart review study that introduced the possibility of selection and/or observation bias, as it was neither randomized nor blinded. Third, patient compliance (or lack thereof) to the post-operative prophylactic regime was not available. Fourth, the information in this study was limited to the specified time within a single institution and there is a possibility of under-reporting that may have played a role, as many DVTs are diagnosed in the outpatient clinic or in the community. Fifth, minor bleeding complications, such as surgical site hematoma and post-operative transfusions, were not recorded in a consistent manner, therefore not included in this study. Sixth, medications purchased over the counter (e.g., aspirin) or provided as samples by physicians were not available in the recorded data. Lastly, a power analysis was not performed since the data were reviewed retrospectively. Further evaluation in a larger randomized controlled study is required to support the findings of this study. The plan is to use these data and perform a quality improvement project to standardize prophylactic anticoagulation strategies after primary TKA in the future.

CONCLUSIONS

Choice of post-operative prophylaxis agents after primary TKA remains an important issue. The observed incidence of symptomatic VTE events in this study is similar to previous literature, regardless of the type of post-operative prophylaxis regimen prescribed after TKA procedure. A higher rate of VTE incidence was observed after completion of apixaban, rivaroxaban, and enoxaparin therapies, suggesting that a longer treatment course may reduce VTE incidence further. In conclusion, the ultimate choice of prophylaxis remains with the treating physician and his or her unique knowledge of a patient’s medical history, especially for patients with known risk factors for VTEs.

REFERENCES


Keywords: deep venous thrombosis, pulmonary embolism, venous thromboembolism, bleeding, total knee arthroplasty.
Patient Controlled Analgesia and an Alternative Protocol: A Comparison of Outcomes After Thoracic and Lumbar Surgery

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ABSTRACT

Introduction. Patient controlled analgesia (PCA) is a common form of pain management after spine surgeries, in which patients get custom control of their opioid dose. PCA has been demonstrated as a safe form of analgesia; however, use of PCA comes with risks that can be mitigated by opting for alternative pain management. This study aimed to compare the outcomes of patients using PCA to those with an alternative analgesia protocol that does not involve PCA.

Methods. A retrospective chart review from January 2017 to July 2018 was conducted. Patients included in this study were those 18 or older who were admitted to a large midwestern tertiary medical center in Wichita, Kansas, and underwent thoracic or lumbar spinal surgery from a single spine surgeon. Data from patient demographics, comorbidities, and type of procedure were collected and compared to control for possible confounding variables. Patients were divided into two groups: patients receiving a PCA pain protocol post-operatively and those receiving a non-PCA protocol. Statistical analyses were performed and all tests with p < 0.05 were considered significant.

Results. This study found patients in the PCA protocol had similar outcomes to those in the alternative analgesia protocol. This was true for both primary and secondary outcomes. The primary outcome was patient length of stay after the operation. Secondary outcomes included readmission rates, frequency of naloxone rescue, transfers to higher levels of care, and total opioid consumption.

Conclusions. This study supported that a non-PCA protocol for post-operative pain management yields similar outcomes to a PCA protocol in the setting of thoracic and lumbar surgery.


INTRODUCTION

More than 238 million opioids were prescribed in the U.S. in 2011, with opioid abuse costing $78.5 billion in healthcare and criminal justice expenditures. In response to an epidemic of opioid-overdoses, government regulations have been tightened, proposals have been made to reduce opioid manufacturing, and there have been manufacturing problems in several pharmaceutical companies. This has resulted in an abrupt shortage of three of the most commonly used parenteral opioids, including hydromorphone (i.e., Dilaudid). The sudden shortage required physicians to adjust their opioid prescribing and find alternative ways to manage patient pain. The Enhanced Recovery After Surgery (ERAS) guideline recommendations urged multimodal analgesia to reduce opioid use post-operatively. The best alternatives, non-steroidal anti-inflammatory drugs (NSAIDs), are a known impediment to bone and ligamentous healing and prevents spinal fusions, which is problematic in the context of spine surgery. A recent study has shown little effect on bone healing in using NSAIDs in the short term. Spine protocols have been slow to add multimodal analgesia, but Cozowicz et al. noted that adding NSAIDs/COX-2 inhibitor to opioids was associated with reduction in opioid prescriptions, cost, and length of hospitalization, and there was an increased use of naloxone by 50% when gabapentinoid was used.

Effective opioid analgesia administration is a difficult balancing act, challenging physicians to ensure proper stewardship of these drugs. On one hand, a large portion of those who become opioid dependent are first exposed in the perioperative period. Conversely, inadequate perioperative analgesia is a risk factor for developing chronic pain, which itself contributes to opioid abuse.

One way to administer opioids in the hospital is by patient-controlled analgesia (PCA). PCA involves patient self-administration (by pushing a button) of small doses of opioids intravenously by means of a programmable pump. Though PCA generally is characterized as being safe, potential problems arise, like pump programming errors, activation of the PCA pump by others (i.e., family members), and equipment failure, resulting in spontaneous activation of drug delivery.

Although studies have demonstrated the risks and benefits of PCA opioid administration, the literature was lacking information comparing patient outcomes between PCA protocols to non-PCA protocols within spine surgery. Specifically, there was limited information comparing the effectiveness of using different administration modalities of opioids post-operatively.

This was a retrospective study to compare patient outcomes from thoracic and lumbar surgeries between patients using a PCA pain control protocol and patients using a non-PCA pain control protocol. The primary outcome used to assess the differences in analgesia was patient length of stay in the hospital. Secondary outcomes included total opioid consumption and the proportion of patients who were readmitted, required naloxone rescue, and transferred to higher levels of care.

METHODS

Participants. Patients included in this study were those 18 years or older who were admitted to a large midwestern tertiary medical center in Wichita, Kansas that performs more than 300 thoracic and lumbar procedures annually. These patients underwent thoracic or lumbar spinal surgery between September 1, 2016 and July 31, 2018. Patients who underwent a thoracic or lumbar procedure between September 1, 2016 and November 16, 2017 used PCA for pain control post-operatively. Patients who underwent a similar procedure between September 1, 2016 and July 31, 2018 were compared to those patients using non-PCA pain control protocol. Statistical analyses were performed and all tests with p < 0.05 were considered significant.
November 30, 2017 and July 31, 2018 predominantly were given oral analgesia (non-PCA) to control pain post-operatively. Patients with the non-PCA protocol could receive parenteral morphine for pain that was not controlled sufficiently on oral analgesia, but this morphine was not administered via PCA. Patients with kidney disease (defined as a glomerular filtration rate less than 60 mL/min) required restricted opioid use, so these patients were excluded from the study.

**Opioid Protocols.** The non-PCA pain management protocol was standardized to the patient taking 1-2 tablets orally every 4-6 hours PRN of hydrocodone 10/325 mg for pain on a scale of 1-5. If the patient still had pain, the hydrocodone 10/325 mg could be switched with 1-2 tablets orally every 4-6 hours PRN of oxycodone (Percocet®) 10/325 mg, for pain on a scale of 1-5. Intravenous (IV) pain medications included 2-4 mg of morphine every hour PRN for pain on a scale of 6-10. However, if pain continued, then the morphine could be switched out with 0.2-0.5 mg every hour PRN of hydromorphone for pain on a scale of 6-10. Lastly, a cyclobenzaprine, or muscle relaxer, was added for the patient to take 10 mg orally every 8 hours to help with muscle spasms.

The PCA pain management protocol was standardized to allow the patient to self-administer IV opioid analgesics via pump and was used as the basis of protocol for this research. There was no loading dose or continuous IV fusion used. The patient was able to self-administer 0.1-0.4 mg of hydromorphone at a range of 5-15 minutes. With PCA, 0.5-2 mg of morphine at a range of 5-15 minutes was a rare substitute for hydromorphone.

**Data Collection.** The abstracted data included patient characteristics such as age, sex, race, and body mass index (BMI); the type of procedure performed; comorbidities (smoking, diabetes, hypertension); and the method of analgesia used post-operatively. Outcome data included: patient length of stay (from surgery to discharge), unplanned hospital readmission within 30 days after discharge, requirement of pain management from the emergency department of one facility within 30 days of the procedure, transfer to a high level of care (intensive care unit, ICU) post-operatively, post-operative naloxone use, and total opioid consumption.

Six different narcotic drugs were abstracted. Four of the narcotics administered were given orally (hydrocodone/Norco®, oxycodone/Percocet®, tramadol, and oxycodone as single formulation), and two were given intravenously (hydromorphone and morphine).

**Procedures.** This project was approved by the Wichita Medical Research and Education Foundation’s Institutional Review Board and the Human Subjects Committee at the University of Kansas School of Medicine–Wichita. Data were collected through a retrospective chart review of eligible patients’ electronic medical records and entered into Research Electronic Data Capture (REDCap®) hosted at University of Kansas School of Medicine–Wichita.

**Statistical Analysis.** Descriptive statistics were summarized using frequencies (percentages) and means (standard deviations). Differences in study variables were compared according to the method of analgesia used post-operatively and analyzed using Pearson’s chi-square, likelihood ratio chi-square, and Fisher’s exact tests, as appropriate. Mean comparisons were conducted using independent t-test, Mann-Whitney U test, and one-way ANOVA was used to compare the means differences as appropriate. Least-squares means (to estimate the marginal means over a balanced population) were used for pairwise comparisons of groups by Tukey test using Kramer adjustment. All statistical tests at p < 0.05 were considered to be significant.

**RESULTS**

Of the 269 patients who met the inclusion criteria, 18 had kidney disease due to the interference with drug metabolism and were excluded. The remaining 251 patients were included in the study analysis: 48.2% (n = 121) in the PCA protocol group and 51.8% (n = 130) in the non-PCA protocol group.

Most patients were Caucasian (92%, n = 231) and female (62%, n = 155), and the average age was 62 years (SD = 13; Table 1). There were no significant differences between the two groups. Other patient characteristics (type of procedure performed, BMI, smoking, diabetes, and hypertension status) were also similar between groups.

The amount of orally administered drugs was similar between the two groups (Table 2), whereas the amount of intravenously administered drugs differed between groups. Those on the PCA protocol received more hydromorphone and less morphine than those on the non-PCA protocol (p < 0.0001).

The average length of stay was 3.66 (95% CI: 3.39-3.93) days for those on the PCA protocol and 3.41 (95% CI: 3.18-3.63) days for those on the non-PCA protocol (p = 0.15). The proportion of 30-day emergency department visits for pain, 30-day inpatient readmission, transfers to the ICU, and naloxone use were not significantly different between the two groups (Table 3).

**DISCUSSION**

The purpose of this study was to compare outcomes between patients using a PCA pain control protocol versus patients using a non-PCA pain control protocol. Findings revealed there were no differences in patient lengths of stay, readmission rates, transfers to higher levels of care, and frequency of naloxone rescue between patients on the PCA and non-PCA protocols. The average amount of narcotic received between the two groups was also similar, except for morphine and hydromorphone. Patients on the PCA protocol received more hydromorphone than patients on the non-PCA protocol due to the hydromorphone shortage; those on the non-PCA protocol received more morphine than those on the PCA protocol since morphine was the parenteral drug used in place of hydromorphone.

There are some advantages of a non-PCA protocol versus a PCA protocol. Although PCA pumps generally are regarded as safe and effective, there have been PCA pump mishaps that have led to patient harm. Though these instances were relatively rare, their risk of occurring was null by removing the PCA pump altogether. Another possible advantage of a non-PCA protocol is a reduced cost compared to using a PCA protocol. By not using the PCA pump, this infers a lower cost compared to a non-PCA alternative because the cost of the pump is avoided. Furthermore, the cost of the drugs between the
### Table 1. Demographics and clinical characteristics of sample population.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total (n = 251)</th>
<th>PCA (n = 121; 48%)</th>
<th>Non-PCA (n = 130; 52%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, years; (SD)</td>
<td>62 (13)</td>
<td>62 (12)</td>
<td>61 (14)</td>
<td>0.65</td>
</tr>
<tr>
<td>Age, range (years)</td>
<td>19-86</td>
<td>22-86</td>
<td>19-83</td>
<td></td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>155 (62)</td>
<td>73 (60)</td>
<td>82 (63)</td>
<td>0.65</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>White</td>
<td>231 (92)</td>
<td>113 (93)</td>
<td>118 (91)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>20 (8)</td>
<td>8 (7)</td>
<td>12 (9)</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Underweight (&lt; 18.5)</td>
<td>5 (2)</td>
<td>2 (2)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Normal weight (18.5-25)</td>
<td>29 (12)</td>
<td>12 (10)</td>
<td>17 (13)</td>
<td></td>
</tr>
<tr>
<td>Overweight (25-30)</td>
<td>62 (25)</td>
<td>24 (20)</td>
<td>40 (31)</td>
<td></td>
</tr>
<tr>
<td>Obese (&gt; 30)</td>
<td>153 (61)</td>
<td>83 (68)</td>
<td>70 (54)</td>
<td></td>
</tr>
<tr>
<td>Clinical Characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic (%)</td>
<td>61 (24)</td>
<td>33 (27)</td>
<td>28 (22)</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>160 (64)</td>
<td>81 (67)</td>
<td>79 (61)</td>
<td>0.31</td>
</tr>
<tr>
<td>Smoking Status (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Never smoked</td>
<td>134 (54)</td>
<td>72 (60)</td>
<td>62 (48)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>81 (32)</td>
<td>34 (28)</td>
<td>47 (36)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>36 (14)</td>
<td>15 (12)</td>
<td>21 (16)</td>
<td></td>
</tr>
<tr>
<td>Procedure Type (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>Non-fusion</td>
<td>50 (20)</td>
<td>26 (21)</td>
<td>24 (18)</td>
<td></td>
</tr>
<tr>
<td>1-2 level fusion</td>
<td>159 (63)</td>
<td>76 (63)</td>
<td>83 (64)</td>
<td></td>
</tr>
<tr>
<td>3+ level fusion</td>
<td>42 (17)</td>
<td>19 (16)</td>
<td>23 (18)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Comparison of narcotics used between PCA and non-PCA groups.

<table>
<thead>
<tr>
<th>Oral</th>
<th>PCA</th>
<th>Non-PCA</th>
<th>MME</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>PCA</td>
<td>Non-PCA</td>
<td>MME</td>
<td>p Value</td>
</tr>
<tr>
<td>Hydrocodone (Norco*©)</td>
<td>99.86 (80.06-119.70)</td>
<td>101.90 (83.21-120.60)</td>
<td>40-120</td>
<td>0.86</td>
</tr>
<tr>
<td>Oxycodone (Percocet*©)</td>
<td>51.90 (35.28-68.52)</td>
<td>52.00 (34.30-69.70)</td>
<td>60-180</td>
<td>0.99</td>
</tr>
<tr>
<td>Tramadol</td>
<td>5.38 (-2.32-13.08)</td>
<td>16.73 (4.78-28.68)</td>
<td>0.08</td>
<td>0.12</td>
</tr>
<tr>
<td>Oxycodone (single formulation)</td>
<td>5.08 (-0.50-10.67)</td>
<td>0.58 (-0.56-1.72)</td>
<td>60-180</td>
<td>0.12</td>
</tr>
<tr>
<td>Intravenous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid*©)</td>
<td>6.59 (5.08-8.09)</td>
<td>1.01 (0.50-1.51)</td>
<td>19.2-48</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.08 (-0.08-0.25)</td>
<td>4.63 (2.82-6.44)</td>
<td>48-96</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Note: All values presented in means and 95% Confidence Intervals; all narcotic values in milligrams. MME stands for Morphine Milligram Equivalence. The Opioid Conversion Calculator from Oregon Pain Guidance was used to calculate the MME per day.

### Table 3. Outcomes of primary and secondary endpoints.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Total (n = 251)</th>
<th>PCA (n = 121; 48%)</th>
<th>Non-PCA (n = 130; 52%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Hospital Length of Stay (days), (SD)</td>
<td>3.53 (1.40)</td>
<td>3.66 (1.49)</td>
<td>3.41 (1.29)</td>
<td>0.15</td>
</tr>
<tr>
<td>Naloxone Use (%)</td>
<td>6 (2)</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>0.92</td>
</tr>
<tr>
<td>Transfer to ICU (%)</td>
<td>5 (2)</td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>0.15</td>
</tr>
<tr>
<td>30-day ED visit for pain (%)</td>
<td>6 (2)</td>
<td>4 (3)</td>
<td>2 (2)</td>
<td>0.36</td>
</tr>
<tr>
<td>30-day Readmission (%)</td>
<td>9 (4)</td>
<td>3 (2)</td>
<td>6 (5)</td>
<td>0.36</td>
</tr>
</tbody>
</table>
two protocols was similar due to each group using a similar amount of narcotics. However, the PCA protocol used more hydromorphone, the non-PCA protocol used more morphine. Morphine is a significantly cheaper opioid than hydromorphone (at this institution, 4 mg of morphine cost $1.67 and 4 mg of hydromorphone cost $7.32); it was also a less potent sedative.19 Hydromorphone delivers 4 morphine milligram equivalents (MME).20 This means hydromorphone is four times as potent as morphine, therefore, the PCA protocol received a higher dose of narcotic overall. The PCA protocol received 26.36 MMEs in hydromorphone, compared to 4.04 MMEs in the non-PCA protocol, making morphine both a cheaper and safer option in comparison to hydromorphone.

An advantage to using a PCA instead of a non-PCA protocol is patient satisfaction. Patients generally are satisfied with the PCA and the feeling of autonomy it provides.10 A disadvantage of a non-PCA protocol is an increased burden on the nursing staff caring for these patients. Since patients without a PCA pump can receive their pain medications only when they are administered by a nursing staff member, an assumption can be made that nursing workloads would increase. Further studies could test this assumption. However, patients on PCA or non-PCA protocols still required routine monitoring.

Decreasing length of stay has been identified as an important measure for increasing hospital efficiency and reducing iatrogenic morbidity and mortality and was a leading factor in the development of current Enhanced Recovery After Surgery (ERAS) guidelines.9,21 Our study found no difference in the length of stay between a PCA and non-PCA protocol, adding to previous studies that suggested there was no difference in length of stay between patients on PCA and non-PCA protocols.10,22

Limitations. Some limitations of the current study included sample size. For a difference of 0.25 days in hospital length of stay to be statistically significant, 500 patients’ data would have to be abstracted (power = 0.80). Adequacy of analgesia in the acute period after surgery is especially important to prevent chronic pain in the context of the current opioid crisis,3 however, our study was not designed to assess this. The current study also failed to distinguish between those patients who were opioid naïve and those who had significant prior exposure. Stratifying according to opioid naïveté versus tolerance would have allowed for elimination of this as a cofounder.

CONCLUSIONS

This study suggested a non-PCA analgesia protocol can result in similar outcomes to a PCA protocol among patients undergoing thoracic or lumbar surgery. A surgeon considering avoiding PCA postoperatively can do so with similar outcomes.

ACKNOWLEDGMENTS

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REFERENCES


Keywords: patient controlled analgesia, opioids, thoracic, lumbar, surgery, length of stay.
The Association of Metabolic-Associated Fatty Liver Disease with Clinical Outcomes of COVID-19: A Systematic Review and Meta-Analysis


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2Creighton University Medical Center, Omaha, NE Department of Internal Medicine
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6Centura Healthcare, Denver, CO Division of Gastroenterology

ABSTRACT

Introduction. Metabolic-associated fatty liver disease (MAFLD) is a hepatic manifestation of metabolic syndrome (MS). MAFLD patients have a higher prevalence of COVID-19. MAFLD also is associated with worse clinical outcomes of COVID-19, such as disease severity, intensive care unit (ICU) admission rate, and higher mortality rates. However, this evidence has not been well characterized in the literature. This meta-analysis aimed to determine the clinical outcomes of COVID-19 among MAFLD patients compared to the non-MAFLD group.

Methods. A comprehensive search was conducted in the Cumulative Index of Nursing and Allied Health (CINAHL), PubMed, Medline, and Embase for studies reporting MAFLD prevalence among COVID-19 patients and comparing clinical outcomes such as severity, ICU admission, and mortality among patients with and without MAFLD. The pooled prevalence of MAFLD among COVID-19 patients and the pooled odds ratios (OR) with 95% confidence intervals (CI) for clinical outcomes of COVID-19 were calculated.

Results. Sixteen observational studies met inclusion criteria involving a total of 11,484 overall study participants, including 1,746 MAFLD patients. The prevalence of COVID-19 among MAFLD patients was 0.29 (95% CI: 0.19-0.40). MAFLD was associated with the COVID-19 disease severity OR 3.07 (95% CI: 2.30-4.09). Similarly, MAFLD was associated with an increased risk of ICU admission compared to the non-MAFLD group OR 1.46 (95% CI: 1.12-1.91). Lastly, the association between MAFLD and COVID-19 mortality was not statistically significant OR 1.45 (95% CI: 0.74-2.84).

Conclusions. In this study, a high percentage of COVID-19 patients had MAFLD. Moreover, MAFLD patients had an increased risk of COVID-19 disease severity and ICU admission rate.

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COVID-19 patients. Similarly, metabolic diseases also were associated with adverse COVID-19 outcomes. However, limited data were available on how MAFLD was associated with the increased prevalence, severity, hospital course, and mortality of COVID-19. Therefore, this meta-analysis evaluated the prevalence of MAFLD among COVID-19 patients and how MAFLD influenced the hospitalization course and severity of COVID-19. The effect of MAFLD on the rate of intensive care unit (ICU) admission and mortality outcomes among COVID-19 patients also was evaluated.

METHODS

Study Search and Selection. The systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement. The study search was conducted in the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed/Medline, Google Scholar, Lilacs, and Embase from the database inception through May 28th, 2021. Potentially relevant articles also were identified by the manual search of the references of the selected articles. The search strategy was designed using keywords to retrieve the articles that demonstrated the association between MAFLD and COVID-19. Moreover, the bibliographies of relevant and review articles were searched manually to include any other studies of interest. The literature search was restricted to the English language articles. The initial screening of the retrieved articles was conducted based on their title and abstracts for possible eligibility. Furthermore, title and abstract-based retrieved articles were assessed for inclusion based on their full-text review. Covidence software (Covidence systematic review software; Veritas Health Innovation: Melbourne, Australia) was used by the two independent researchers (UH, MZA) to assess the eligibility of articles for final inclusion.

Inclusion Criteria. The studies were included in the final meta-analysis if they met the following inclusion criteria: (a) epidemiological studies involving patients older than 18 years of age, (b) reported laboratory-confirmed COVID-19 cases, (c) reported prevalence of MAFLD among the COVID-19 patients, (d) reported possible association risk between MAFLD and COVID-19 disease severity, ICU admission, and mortality. The following keywords were used for search strategy in PubMed, CINAHL, and Embase: "COVID-19" or "COVID-19/ mortality", and "COVID-19" or "coronavirus", and "NAFLD" or "non-alcoholic fatty liver disease", and "MAFLD" or "metabolic associated fatty liver disease". MAFLD was defined by the presence of hepatic steatosis and three other measures, including the presence of DM2, obesity, and evidence of body metabolic dysregulation. COVID-19 patients were considered to have the severe disease when they met the following criteria: (1) hypoxia (oxygen saturation less than 92%), (2) increased respiratory rate (greater than 35 per minute), (3) decreased consciousness: somnolence, apathy, convulsions, and coma, (4) certain specific manifestations, such as bleeding, coagulation disorders (deep venous thrombosis, pulmonary embolism), cardiovascular manifestation such as myocardial infarction, abnormally raised liver enzymes, rhabdomyolysis, and gastrointestinal dysfunction such as severe diarrhea.

Exclusion Criteria. The studies with patients younger than 18 years, pregnant patients, and those lacking informed consent were excluded. Also, those studies with a secondary cause of fatty liver diseases, such as alcoholic liver disease, autoimmune liver disease, drug-induced liver injury, cholestatic liver disease, and viral hepatitis, were excluded. Furthermore, interventional trials, animal studies, reviews, case reports, genetic studies, commentary, and study protocols were excluded. Lastly, this meta-analysis did not include the studies with incomplete literature data or information, study definitions, or unclear descriptions of outcomes.

Data Extraction. The following data were collected from each publication selected: (1) the characteristics of the study population including age, sex, body mass index (BMI), MAFLD and COVID-19 assessment methods, and population co-morbidities, (2) author name, study year, country of publication, trial registration, type of observational studies, source of the included database, duration of study follow-up, and the proportion of COVID-19 study population with metabolic associated fatty liver disease, and (3) study outcomes such as effect estimates of odds ratio (OR), risk ratio (RR), and hazard ratio (HR) were reported. To conform with the newer MAFLD definition, unadjusted ORs (not adjusted for other covariates such as age, sex, ethnicity, race, BMI, and other co-morbidities (e.g., hypertension, diabetes mellitus, obesity smoking, cardiovascular diseases, hepatocellular carcinoma (HCC), dyslipidemia, COPD, and alcohol consumption)) were used from those studies which reported the association between NAFLD and COVID-19 clinical outcomes. The absolute number of COVID-19 patients within the MAFLD and non-MAFLD group, along with the study conclusion, also were extracted. Any conflicts in the initial study screening process and data extraction phase were resolved by consensus and discussion with the senior author (MA).

Quality Assessment. The included studies were assessed for quality. The Newcastle–Ottawa scale (NOS) was used. Three parameters of the scale, such as selection, comparability, and outcome/exposure, were applied to assess the quality of the publications. The studies were classified as low, medium, or high quality according to the NOS scale achieved based on the three parameters (e.g., selection, comparability, and outcome/exposure). The quality assessment was performed by two authors (UH, MZA) independently, and any discrepancies were resolved through mutual consensus. All studies with a higher NOS score (based on selection, comparability, and outcome/exposure) were selected. A high score indicates a high study quality.

Statistical Analysis. Meta-analysis was performed using the RStudio software (RStudio, v4.1.0; University of Auckland, New Zealand). The pooled prevalence of MAFLD among COVID-19 patients was calculated. The study used the published studies’ available effect estimates of OR, HR, and RR. Absolute numbers were used to calculate the unadjusted ORs if the effect estimate was not reported. Pooled OR with 95% confidence intervals (CI) were calculated to assess the pooled estimates of odds of COVID-19 disease severity, ICU admission rate, and mortality (reference group: patients without MAFLD). A random-effect model was used to pool the effect estimates, based on the heterogeneity assessment of the individual study effect
estimate. A p value of < 0.05 was considered statistically significant for the pooled effect estimates. Forest plots were utilized to demonstrate the results of the meta-analysis.

Heterogeneity between the studies was tested with F and X² tests for Cochran Q statistics. According to Cochran’s handbook, F value of (0-40%) was interpreted as “might not be important,” (30-60%) as “moderate,” (50-90%) as substantial, and (70-100%) as considerable heterogeneity.20,21 The statistical review of this study was conducted by author UH.

RESULTS

The search results covered the period of database inception from December 2019 through May 2021. The total search results were 244 items, and after removing duplicates, it was reduced to 203. Fifty-eight studies were included in the full-text review process (by UH and MZA). After a full-text review of the extracted articles, sixteen studies were selected for the final meta-analysis, involving 11,484 overall study participants, including 1,746 MAFLD patients (Figure 1).

Figure 1. PRISMA flow chart of the studies.

Characteristics of the Studies Included. Three studies were cross-sectional or case-control studies,23-25 and 13 articles were retrospective cohort studies.22-26,28,30,31,34-40 Eight studies were reported from China,24-26,29,31,34-36 three were from the U.S.,22,29,36 two from the UK,32,35 one from Turkey,25 one from Mexico,38 and one from Israel.21 All studies were conducted between December 2019 and May 2021. The data sources for all studies were mainly electronic medical records/health records (EMR/HR).

Of the total, eight studies confirmed fatty liver disease based on ultrasound or computer tomography (CT).23,24,26,28,30,31,35,36 Three studies used new consensus definition of MAFLD for diagnosis,23,26,30 four studies used hepatic steatosis index (HIS),29,38-40 one study used international classification disease code (ICD).21 Two studies reported MAFLD based on the confirmed diagnosis of DM2 and obesity.23,32 One study reported MAFLD based on EMR/HR.25 The significant co-morbidities reported across all the included studies were obesity, DM2, hypertension, dyslipidemia, ischemic heart disease, chronic lung disease, chronic kidney disease (CKD), and metabolic dysregulation (see Tables 1 and 2 available online only at journals.ku.edu/kjm). Ten studies used reverse transcriptase-polymerase chain reaction (RT-PCR) to diagnose COVID-19 infection.23,26,28,30,32,33,36,38 Six studies used laboratory-confirmed cases of COVID-19 infection.22,24,25,28,39,40 One study did not provide clear information about the COVID-19 diagnosis method.26

MAFLD prevalence in COVID-19 patients. All sixteen studies reported the MAFLD prevalence in COVID-19 patients. The pooled prevalence of COVID-19 among MAFLD patients was 0.29 (95% CI: 0.19-0.40; p < 0.001; Figure 2).

Figure 2. Forest plot of the pooled prevalence of the MAFLD among COVID-19 patients. OR, odds ratio; CI, confidence interval.

Clinical Outcomes

COVID-19 Severity in Patients with MAFLD. Twelve studies reported the severity of the COVID-19 symptoms related to MAFLD.22-26,28,30,32,33,36,38,40 The pooled OR for severe COVID-19 symptoms in patients with MAFLD was 3.07 (95% CI: 2.30-4.09; p = 0.04) compared to those without MAFLD (Figure 3). Six studies reported the disease outcome as the severity of COVID-19 in MAFLD patients compared to those without MAFLD.29,31,33,38,42 Another six studies reported the outcome as COVID-19 severity among NAFLD patients.22,23,24,26,39,40 One study reported the association of obesity and metabolic dysregulation with COVID-19 severity.35 Targher et al.24 determined the association of COVID-19 severity with both low and high FIB-4 (hepatic fibrosis) scores. Also, Zhou et al.26 reported the association of COVID-19 severity with NAFLD in both young and older patients separately.

COVID-19 Rate of ICU Admission in Patients with MAFLD. Overall, four studies reported the association between MAFLD and the rate of ICU admission among COVID-19 patients.29,31,36,38 There was a significant increase in the rate of ICU admission among patients with MAFLD compared to those without. The pooled estimated OR was 1.46 (95% CI: 1.12-1.91; p = 0.28; Figure 4). The statistical heterogeneity for this analysis measured by I² was 22%. The clinical characteristics and quality assessment of the included studies have been described in Table 1 (available online only at journals.ku.edu/kjm).
COVID-19 Mortality in MAFLD. Seven studies reported the COVID-19 mortality among MAFLD patients compared to those without MAFLD.\textsuperscript{22,29,31,33,35,36,38} There was no observed statistical difference in the COVID-19 mortality among MAFLD patients compared to those without (OR 1.45; 95% CI: 0.74-2.84; p = < 0.01; Figure 5). The clinical characteristics and quality assessment of the included studies have been described in Table 1 (available online only at journals.ku.edu/kjm).

### DISCUSSION

The meta-analysis and systemic review have demonstrated the MAFLD prevalence and outcomes of COVID-19 among patients with MAFLD compared to those without. The study findings have established a high risk of COVID-19 disease severity and ICU admission among the patients with MAFLD than those without MAFLD. Moreover, there was an increased risk of COVID-19 mortality among MAFLD patients than those without MAFLD; however, this finding did not reach statistical significance.

COVID-19 is caused by SARS-CoV-2, which is genetically related to other coronavirus families such as SARS-CoV and Middle Eastern respiratory syndrome coronavirus (MERS-CoV). These coronaviruses are known to affect liver function by different mechanisms. The direct effect of these viruses through translocation from the gut to the liver can spoil liver function. SARS-CoV-2 binds to the liver cells through angiotensin-converting enzyme receptors and causes direct toxicity through active viral replication within the hepatic cells. Furthermore, SARS-CoV-2 also can affect liver function through indirect mechanisms (e.g., causing ischemia, inflammation). According to the cytokine storm hypothesis, SARS-CoV-2 infection can cause a severe immune-mediated cytokine storm because of inflammation that can damage the hepatocytes. This hypothesis was supported by the rise of the blood levels of the pro-inflammatory markers IL-2, IL-4, low-density lipoprotein, C-reactive protein, and serum ferritin in COVID-19 patients. Among the other possible mechanisms of liver injury included drug-induced liver damage. Most of these patients were treated with antiviral drugs that can have harmful effects on hepatocytes, resulting in a rise in ALT and AST.\textsuperscript{41,45}
The liver has an abundance of innate immune cells (e.g., macrophages, natural killer T cells, and γδ T cells). Comorbid conditions such as obesity and MAFLD have been associated with the increased production of pro-inflammatory cytokines like tumor necrosis factor-α from Kupffer and adipose cells. In MAFLD, free fatty acids flux in the hepatocytes and adipose tissue insulin resistance activates the liver macrophages. The dysregulated macrophages response in the liver of MAFLD patients promotes inflammation leading to the progression and severity of COVID-19.

The presented meta-analysis revealed the high pooled prevalence of MAFLD among COVID-19 patients. This finding was comparable with the previously reported literature. In a meta-analysis of four studies, Pan et al. reported a pooled prevalence of 0.31 (95% CI: 0.28-0.35) of MAFLD among COVID-19 patients. Moreover, the current study revealed a higher risk of COVID-19 disease severity among MAFLD patients than those without MAFLD. These findings were in aligned with other published studies. Hegyi et al. reported an association of MAFLD with COVID-19. They demonstrated that MAFLD was associated with an increased risk of COVID-19 disease severity compared to the non-MAFLD group (OR = 2.61 [95% CI: 1.75-3.91]).

Similarly, Singh et al., in a pooled analysis, found that the presence of MAFLD among COVID-19 patients is associated significantly with a higher risk of COVID-19 severity and ICU admission. Another study reported that obesity alone was associated with a significantly increased risk of COVID-19 disease severity even after adjusting for other confounders and co-morbidities. The current meta-analysis revealed the effect of MAFLD on COVID-19 severity by using a large cohort of studies.

This study had limitations that need to be considered while interpreting the results. First, the respective studies included in this meta-analysis lacked a robust and consistent definition of COVID-19 disease severity. However, this limitation can be recommended for future epidemiological studies to contemplate while determining an association between COVID-19 outcomes and MAFLD. Furthermore, the various included studies did not adjust for confounding factors such as age, race, sex, and certain other co-morbidities, which can affect the study findings. Moreover, the study population had several co-morbidities, such as hypertension, obesity, DM2, CVD, and CKD, making it challenging to dissect the contribution of each co-morbidity towards COVID-19 outcomes, as previous studies have shown the negative association of these co-morbidities with COVID-19. Lastly, fewer studies were included in the sub-group analysis of the effect of MAFLD on COVID-19 ICU admission rate and mortality, which made it challenging to analyze publication bias (less than ten articles). Despite the limitations, this study merits consideration. Foremost, to the best of our knowledge, this was the first study to report the MAFLD prevalence and COVID-19 outcomes together in a large-scale MAFLD population. In addition, this study is the first to report the COVID-19 mortality among MAFLD patients in a large cohort of studies.

CONCLUSIONS

In conclusion, MAFLD was more prevalent among patients with COVID-19. This meta-analysis and systemic review revealed a higher risk of COVID-19 disease severity and ICU admission in patients with MAFLD than their counterparts; however, the association between MAFLD and COVID-19 mortality was not significant. These findings suggested that the MAFLD patients should be followed closely for these complications if they develop COVID-19. The potential mechanism of COVID-19 severity among MAFLD patients remains illuminated by future studies. Furthermore, extensive prospective cohort studies are needed to include ICU admission rate and mortality outcomes in COVID-19 patients to elucidate the impact of MAFLD further.

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Comprehension Profile of Patient Education Materials in Endocrine Care
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1University of Missouri–Kansas City, School of Medicine, Kansas City, MO
Division of Endocrinology
2Wayne State University School of Medicine, Detroit, MI

ABSTRACT

Introduction. The internet is an ever-evolving resource to improve healthcare literacy among patients. The nature of the internet can make it difficult to condense educational materials in a manner applicable to a worldwide patient audience. Within the realm of endocrinology, there is lack of a comprehensive analysis regarding these pathologies in addition to education materials related to their medical work-up or management. The aim of this study was to assess contemporary online patient education material in endocrinology and management of care.

Methods. Analysis of the readability of 1,500 unique online education materials was performed utilizing seven readability measures: Flesch Reading Ease (FRE), Flesch-Kincaid Grade Level (FKGL), Gunning Fog Index Readability Formula (FOG), Simple Measure of Gobbledygook Index (SMOG), Coleman-Liau Index (CLI), automated readability index (ARI), and Linsear Write Formula (LWF).

Results. The average grade level readability scores from six measures (e.g., FKGL, FOG, SMOG, CLI, ARI, LWF) was more than or equal to 11 which corresponds to a reading level at or above the 11th grade. The average FRE between adrenal, diabetes, and thyroid-related education material ranged between “fairly difficult” to “very difficult”.

Conclusions. The readability of contemporary online endocrine education material did not meet current readability recommendations for appropriate comprehension of the general audience.


INTRODUCTION

The internet remains a primary source for self-education among patients regarding health-related content. Moreover, the literature established a high level of patient satisfaction in the reported use of internet-based sources in seeking this self-education.1 This satisfaction largely stems from the convenience of immediate information retrieval utilizing internet-based search queries. This convenience led to patients with a proactive approach to their own healthcare and ultimately greater involvement in making patient centered medical decisions with their healthcare providers.2

The concept of healthcare literacy is tied closely with the health of an individual. Poor healthcare literacy was associated with poor self-reported health conditions, increased risk for hospital admissions, and greater healthcare costs.3 However, the ever-evolving material found through the internet can be difficult to condense in a manner applicable for the worldwide audience to work efficiently into their own healthcare literacy.3 The concept of the readability of patient education material serves an important role in a person’s ability to comprehend the material and plays a direct role in their healthcare literacy.7 It is recommended that the readability of patient education materials should not be higher than sixth-to-eighth-grade reading level.8 Moreover, the National Institutes of Health recommended the readability of self-administered patient questionnaires to be written no more than a sixth-grade reading level.9 However, the implementation of this readability recommendation is more difficult with regard to the internet due to lack of peer-review and regulatory factors which can aid in the authentication and validity of online patient educational materials.10

This imbalanced relationship between the immense usage of the internet and readability recommendations highlighted the necessity for further understanding of this climate of online information.11 The current literature, which investigated the readability of online patient education materials, have shown failure to meet these established readability recommendations, and it was supported that current healthcare literacy must be improved upon to improve healthcare outcomes holistically.12-14

Within the field of endocrinology, the use of information in real-time is key for providers to guide the management of patients with endocrine and metabolic diseases and has led to greater advancement of patient care technology (i.e., eHealth apps, advancements in continuous glucose monitors).15-19 Despite this, there was a paucity of data which provided a comprehensive readability assessment of endocrine-related care. Moreover, current endocrine readability literature often was isolated to pathology or metabolic conditions.20-28 This limited real time comparative analytic data which can help endocrine providers in providing improved health care education.29-30 Therefore, the aim of this study was to assess contemporary online patient education material in endocrine disorders and management of care.

METHODS

Ethics. The data utilized in this study was entirely available for public use and did not involve human subjects. Therefore, Institutional Review Board approval was not required for this study.

Screening. Between November 2021 and January 2022, online education materials were extracted from Google® search queries (Google Inc., Mountain View, CA) for endocrine-related content areas of interest. Among these queries, three primary categories of content were of interest: adrenal, diabetes, and thyroid. These three categories of endocrine-related content were chosen due to perceived paucity of literature to date. Within each category, there were 10 common search items relevant for the category which were used in the queries as outlined in Table 1. These search items were chosen based on review of the most recent literature produced by the World Health Organization for the three categories.31-33

Each search item was entered individually as a search query and the first 50 site link results which met the study’s inclusion and exclusion criteria were utilized in the analysis. For the purpose of this study, sites were included if they contained content that was pertinent towards providing general information on the search query of interests, as evaluated by the screeners (SPS, SS, KQ, SM). Sites met inclusion if

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they were in the English language, contained over 250 words minimum, and publicly available without any form of subscription required. Sites were excluded if they underwent a formal peer-reviewed research process with scientific indexing, the site explicitly specified the intended audience is for healthcare providers only, nonfunctioning search links, duplicate links, and/or did not meet the inclusion criteria.

Table 1. Endocrine-related content areas of interest.

<table>
<thead>
<tr>
<th>Adrenal</th>
<th>Diabetes</th>
<th>Thyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s Disease</td>
<td>Type 1 Diabetes</td>
<td>Graves’ Disease</td>
</tr>
<tr>
<td>Cushing’s Disease</td>
<td>Type 2 Diabetes</td>
<td>Hashimoto’s Thyroiditis</td>
</tr>
<tr>
<td>Cushing’s Syndrome</td>
<td>Insulin</td>
<td>Thyroid Hormone</td>
</tr>
<tr>
<td>Conn’s Syndrome &amp; Hyperaldosteronism</td>
<td>Metformin</td>
<td>Thyroid Cancer</td>
</tr>
<tr>
<td>Congenital Adrenal Hyperplasia</td>
<td>Dipeptidyl Peptidase-4 (DPP-4) Inhibitor</td>
<td>Goiter</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Sodium / Glucose Cotransporter (SGLT-2) Inhibitor</td>
<td>Levotyroxine</td>
</tr>
<tr>
<td>Multiple Endocrine Neoplasia</td>
<td>Insulin Pumps</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Sulfonylureas</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Paraganglioneuroma</td>
<td>Diabetic Ketoacidosis</td>
<td>Thyroid Biopsy</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>Maturity Onset Diabetes of the Young</td>
<td>Thyroid and Iodine</td>
</tr>
</tbody>
</table>

Readability Quantification. Upon screening, the site content was reformatted to plain text in Microsoft Word®, as shown in previous literature methodology, to create efficient readability calculations later in the study.24-29 During the reformat phase, content material was removed for plain text if the screeners identified the content was unrelated to patient education. This specifically included removal of acknowledgments, author information, copyright disclaimers, figures and related captions and legends, references, and any web page navigation text. Moreover, the remaining content was unchanged from its site’s original format when converted to individual plain text documents for each site link.

After the reformat phase, each plain text document was evaluated quantitatively for its readability. This was performed through seven readability quantification measurements: Flesch Reading Ease (FRE), Flesch-Kincaid Grade Level (FKGL), Gunning Fog Index Readability Formula (FOG), Simple Measure of Gobbledygook Index (SMOG), Coleman-Liau Index (CLI), automated readability index (ARI), and Linsear Write Formula (LWF). The FRE was utilized in this study as it was one of the oldest and most used readability quantification measurement scales. FRE assesses the readability of the plain text using a scale of 0 to 100 where the higher the scaled number implies a higher readability of the plain text. For categorization purposes, the FRE in this study was scaled based off previous literature: very difficult (0-29), difficult (30-49), fairly difficult (50-59), standard (60-69), fairly easy (70-79), easy (80-89), and very easy (90-100).29-34

Similarly, the FKGL attempts to quantify the plain text by focusing on the average number of words per sentence and average number of syllables per word in the scale to correlate to a grade level (i.e., score of 94 would suggest a U.S. ninth grade reading level).29 The SMOG scale focuses on the total polysyllabic word count of the plain text to correlate to a grade level (i.e., a SMOG of 40 would approximate a U.S. ninth grade reading level). The CLI scale focuses on the average number of characters and sentences per 100 words of plain text (i.e., a CLI of 9.5 would correlate to a U.S. ninth to tenth grade reading level). The ARI is the summation of word and sentence difficulty to quantify a reading level utilizing similar characters per word and words per sentence (i.e., an ARI of 9 would approximate a U.S. ninth grade reading level). The LFW scale focuses on per 100 word sets similar to CLI, but also categorizes syllable counties per word as “easy words” (two or less syllables) or “hard words” (three or more syllables).27-29

The date of the search queries was recorded to limit potential ambiguity in search comparisons. Additionally, the country of origin of the site link was recorded (i.e., United States, United Kingdom). All data were recorded using Microsoft Excel® (Microsoft Corporation, Redmond, WA).

Statistical Analysis. Statistical analysis of the seven readability quantification scales was performed using Stata 14 Statistical Package® (StataCorp, College Station, TX) for descriptive statistics on the variables of interest, including counts, percentages, means, and standard deviations, where appropriate. Confidence intervals (CI) for parametric distribution were set at 95%. One way analysis of variance (ANOVA) was performed to compare average FRE measurements among search items with each category. The level of significance was set at p < 0.05.

RESULTS

Between November 2021 and January 2022, a total of 1,500 educational materials (500 diabetic, 500 adrenal, and 500 thyroid education materials) were quantified for all seven readability assessment measurements for a total of 10,500 calculated measurements. The origin of 88.2% of all education material was the U.S. (n = 1,323), followed by 6.3% of articles from the U.K. (n = 94). The average grade reading level of all education materials was 13.08 (n = 1,500). The average grade reading levels and FRE of each topic of educational material were as shown in Table 2.

Table 2. Average grade reading levels across categories.

<table>
<thead>
<tr>
<th>Content of Education Materials</th>
<th>Average Grade Reading Level</th>
<th>Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes-Related</td>
<td>13.54</td>
<td>(CI: 13.08 - 14.00)</td>
</tr>
<tr>
<td>Thyroid-Related</td>
<td>12.91</td>
<td>(CI: 12.56 - 13.26)</td>
</tr>
<tr>
<td>Adrenal-Related</td>
<td>12.78</td>
<td>(CI: 12.34 - 13.22)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Content of Education Materials</th>
<th>Average Flesch Reading Ease Measurements</th>
<th>Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes-Related</td>
<td>40.29 (“difficult to read”)</td>
<td>(CI: 34.45 - 46.13)</td>
</tr>
<tr>
<td>Thyroid-Related</td>
<td>39.82 (“difficult to read”)</td>
<td>(CI: 36.45 - 43.21)</td>
</tr>
<tr>
<td>Adrenal-Related</td>
<td>32.57 (“difficult to read”)</td>
<td>(CI: 28.17 - 36.97)</td>
</tr>
</tbody>
</table>
These results quantified all educational materials amongst the content categories as being “difficult to read” as per FRE measurements. Among the subgroup analysis of adrenal-related educational materials, no online education materials met at least one measurement of a sixth grade reading level or less (n = 50). In addition, content related to paraganglioneuromas had the highest grade reading level at 16.45 (CI: 15.01 - 17.89). Content related to neuroblastosmas had the lowest grade reading level at 12.18 (CI: 11.84 - 12.54). The average grade reading level of all other adrenal-related content was as shown in Table 3.

Table 3. Reading level analysis of adrenal-related educational material.

<table>
<thead>
<tr>
<th>Content Related To:</th>
<th>Grade Reading Level</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraganglioneuroma</td>
<td>16.45</td>
<td>(CI: 15.01 - 17.89)</td>
</tr>
<tr>
<td>Conn’s Syndrome</td>
<td>14.74</td>
<td>(CI: 14.30 - 15.18)</td>
</tr>
<tr>
<td>Congenital Adrenal Hyperplasia</td>
<td>14.48</td>
<td>(CI: 14.05 - 14.91)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>14.22</td>
<td>(CI: 13.81 - 14.63)</td>
</tr>
<tr>
<td>Multiple Endocrine Neoplasia</td>
<td>13.94</td>
<td>(CI: 13.58 - 14.30)</td>
</tr>
<tr>
<td>Cushing’s Disease</td>
<td>13.18</td>
<td>(CI: 13.14 - 13.22)</td>
</tr>
<tr>
<td>Addison’s Disease</td>
<td>13.16</td>
<td>(CI: 12.84 - 13.48)</td>
</tr>
<tr>
<td>Cushing’s Syndrome</td>
<td>13.12</td>
<td>(CI: 12.77 - 13.46)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>12.18</td>
<td>(CI: 11.84 - 12.54)</td>
</tr>
</tbody>
</table>

Among the analysis of FRE measurements for adrenal-related educational material, Addison’s Disease had the highest FRE measurement at 45.07 (CI: 30.76 - 39.38), which would qualify as “difficult to read”. Likewise, Conn’s Syndrome had the lowest FRE measurement at 21.97 (CI: 16.55 - 27.40), which would qualify as “very difficult to read”. The average FRE of all other adrenal-related content was as shown in Table 4.

Table 4. Average Flesch Reading Ease measurements of adrenal-related education materials.

<table>
<thead>
<tr>
<th>Content Related To:</th>
<th>Flesch Reading Ease Measurement</th>
<th>Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s Disease</td>
<td>45.07 (&quot;difficult&quot;)</td>
<td>(CI: 30.76 - 39.38)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>42.81 (&quot;difficult&quot;)</td>
<td>(CI: 38.54 - 47.08)</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>38.94 (&quot;difficult&quot;)</td>
<td>(CI: 33.75 - 44.13)</td>
</tr>
<tr>
<td>Cushing’s Disease</td>
<td>37.11 (&quot;difficult&quot;)</td>
<td>(CI: 32.96 - 41.25)</td>
</tr>
<tr>
<td>Multiple Endocrine Neoplasia</td>
<td>33.73 (&quot;difficult&quot;)</td>
<td>(CI: 29.87 - 37.59)</td>
</tr>
<tr>
<td>Conn’s Syndrome</td>
<td>29.32 (&quot;very difficult&quot;)</td>
<td>(CI: 23.77 - 34.87)</td>
</tr>
<tr>
<td>Paraganglioneuroma</td>
<td>26.07 (&quot;very difficult&quot;)</td>
<td>(CI: 20.58 - 31.55)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>23.11 (&quot;very difficult&quot;)</td>
<td>(CI: 17.76 - 28.45)</td>
</tr>
<tr>
<td>Conn’s Syndrome</td>
<td>21.97 (&quot;very difficult&quot;)</td>
<td>(CI: 16.55 - 27.40)</td>
</tr>
</tbody>
</table>

Among the subgroup analysis of diabetes-related educational materials, 10% of Type 1 diabetes online education materials met at least one measurement of a sixth grade reading level or less (n = 5), and all others were less than 10%. In addition, content related to sodium/glucose cotransporter 2 (SGLT2) inhibitors had the highest-grade reading level at 14.70 (CI: 14.33 - 15.08). Content related to type 1 diabetes had the lowest grade reading level at 11.15 (CI: 11.85 - 11.45). The average grade reading level of all other diabetes-related content was as shown in Table 5.

Table 5. Average grade reading level of diabetes-related educational material.

<table>
<thead>
<tr>
<th>Content Related To:</th>
<th>Grade Reading Level</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitors</td>
<td>14.70</td>
<td>(CI: 14.33 - 15.08)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>13.87</td>
<td>(CI: 12.99 - 14.76)</td>
</tr>
<tr>
<td>Maturity Onset Diabetes of the Young</td>
<td>13.54</td>
<td>(CI: 13.15 - 13.93)</td>
</tr>
<tr>
<td>Metformin</td>
<td>13.33</td>
<td>(CI: 12.96 - 13.71)</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>13.29</td>
<td>(CI: 12.88 - 13.70)</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>12.04</td>
<td>(CI: 11.10 - 12.99)</td>
</tr>
<tr>
<td>Insulin</td>
<td>12.03</td>
<td>(CI: 11.67 - 12.39)</td>
</tr>
<tr>
<td>Insulin Pumps</td>
<td>11.91</td>
<td>(CI: 11.56 - 12.26)</td>
</tr>
<tr>
<td>Diabetic Ketoacidosis</td>
<td>11.61</td>
<td>(CI: 11.26 - 11.96)</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>11.15</td>
<td>(CI: 11.85 - 11.45)</td>
</tr>
</tbody>
</table>

Regarding FRE measurements for diabetes-related educational material, Type 1 diabetes had the highest FRE measurement at 52.28 (CI: 48.52 - 56.03), which would qualify as “fairly difficult to read”. Likewise, SGLT2 inhibitors had the lowest FRE measurement at 26.10 (CI: 22.80 - 29.39), which would qualify as “very difficult to read”. The average FRE of all other diabetes-related content was as shown in Table 6.

Table 6. Average Flesch Reading Ease measurements of diabetes-related education materials.

<table>
<thead>
<tr>
<th>Content Related To:</th>
<th>Flesch Reading Ease Measurement</th>
<th>Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td>52.28 (&quot;fairly difficult&quot;)</td>
<td>(CI: 48.52 - 56.03)</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>49.46 (&quot;difficult&quot;)</td>
<td>(CI: 46.35 - 52.58)</td>
</tr>
<tr>
<td>Insulin pumps</td>
<td>48.30 (&quot;difficult&quot;)</td>
<td>(CI: 43.94 - 52.67)</td>
</tr>
<tr>
<td>Insulin</td>
<td>47.32 (&quot;difficult&quot;)</td>
<td>(CI: 44.07 - 50.58)</td>
</tr>
<tr>
<td>Diabetic Ketoacidosis</td>
<td>44.91 (&quot;difficult&quot;)</td>
<td>(CI: 40.44 - 49.41)</td>
</tr>
<tr>
<td>Metformin</td>
<td>38.71 (&quot;difficult&quot;)</td>
<td>(CI: 34.36 - 43.06)</td>
</tr>
<tr>
<td>Maturity Onset Diabetes of the Young</td>
<td>34.69 (&quot;difficult&quot;)</td>
<td>(CI: 30.51 - 38.87)</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>32.92 (&quot;very difficult&quot;)</td>
<td>(CI: 28.98 - 36.86)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>28.17 (&quot;very difficult&quot;)</td>
<td>(CI: 24.25 - 37.59)</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>26.10 (&quot;very difficult&quot;)</td>
<td>(CI: 22.80 - 29.39)</td>
</tr>
</tbody>
</table>

Among the subgroup analysis of thyroid-related educational materials, 10% of hyperthyroidism online education materials met at least one measurement of a sixth grade reading level or less (n = 5), and all others were less than 10%. In addition, content related to hyperthyroidism had the highest-grade reading level at 13.73 (CI: 13.29 - 14.17). Content related to thyroid biopsy had the lowest grade reading level at 11.20 (CI: 10.86 - 11.54). The average grade reading level of all other thyroid-related content was as shown in Table 7.
Table 7. Average grade reading level of thyroid-related educational material.

<table>
<thead>
<tr>
<th>Content Related To</th>
<th>Grade Reading Level</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>13.73</td>
<td>(CI: 13.29 - 14.17)</td>
</tr>
<tr>
<td>Graves' Disease</td>
<td>13.18</td>
<td>(CI: 12.84 - 13.52)</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>12.97</td>
<td>(CI: 12.52 - 13.43)</td>
</tr>
<tr>
<td>Hashimoto's Thyroiditis</td>
<td>12.92</td>
<td>(CI: 12.58 - 13.26)</td>
</tr>
<tr>
<td>Thyroid and Iodine</td>
<td>12.91</td>
<td>(CI: 12.51 - 13.30)</td>
</tr>
<tr>
<td>Thyroid Hormone</td>
<td>12.48</td>
<td>(CI: 12.14 - 12.82)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>12.44</td>
<td>(CI: 12.13 - 12.75)</td>
</tr>
<tr>
<td>Goiter</td>
<td>11.61</td>
<td>(CI: 11.32 - 11.89)</td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>11.36</td>
<td>(CI: 11.04 - 11.68)</td>
</tr>
<tr>
<td>Thyroid Biopsy</td>
<td>11.20</td>
<td>(CI: 10.86 - 11.54)</td>
</tr>
</tbody>
</table>

Table 8. Average Flesch Reading Ease of thyroid-related content.

<table>
<thead>
<tr>
<th>Content Related To</th>
<th>Flesch Reading Ease Measurement</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Cancer</td>
<td>47.95 (&quot;difficult to read&quot;)</td>
<td>(CI: 44.20 - 51.70)</td>
</tr>
<tr>
<td>Thyroid Biopsy</td>
<td>47.80 (&quot;difficult&quot;)</td>
<td>(CI: 43.43 - 52.16)</td>
</tr>
<tr>
<td>Goiter</td>
<td>45.98 (&quot;difficult&quot;)</td>
<td>(CI: 42.50 - 49.46)</td>
</tr>
<tr>
<td>Thyroid Hormone</td>
<td>39.11 (&quot;difficult&quot;)</td>
<td>(CI: 35.23 - 42.99)</td>
</tr>
<tr>
<td>Thyroid and Iodine</td>
<td>38.35 (&quot;difficult&quot;)</td>
<td>(CI: 33.82 - 42.88)</td>
</tr>
<tr>
<td>Grave's Disease</td>
<td>37.81 (&quot;difficult&quot;)</td>
<td>(CI: 33.83 - 41.79)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>37.51 (&quot;difficult&quot;)</td>
<td>(CI: 33.64 - 41.39)</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>36.72 (&quot;difficult&quot;)</td>
<td>(CI: 32.24 - 41.21)</td>
</tr>
<tr>
<td>Hashimoto's Thyroiditis</td>
<td>33.56 (&quot;difficult&quot;)</td>
<td>(CI: 29.15 - 37.97)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>33.44 (&quot;difficult&quot;)</td>
<td>(CI: 29.15 - 37.72)</td>
</tr>
</tbody>
</table>

DISCUSSION

The internet remains a form of a “pseudo-provider” due to its essential usage in nearly a third of information-seeking individuals when trying to self-diagnose or manage care without professional consultation.41-43 The growth of information-seeking behavior among individuals created both a beneficial effect in allowing extremely efficient dissemination of information than seen in previous years.44 This allowed a greater number of individuals to become empowered and gain greater awareness, including in healthcare literacy. In addition, that information also may aid in alleviating patient anxiety and involved with risk reduction strategies.45-49 However, this rise in information-seeking behavior has been suggested to cause cognitive changes in our ability to comprehend material and memory, and improper information seeking behavior may be related to risk behaviors including improper drug usage and potential addictions.43,47,50 The rise in these neuropsychological changes make it critical that individuals must be exposed to appropriate, legitimate comprehension to protect themselves.

The findings were in concordance with prior studies on diabetes and management. Moreover, a readability analysis on monogenic diabetes noted search items included in their analysis had failed to meet recommendations of a grade reading level standards of less than the sixth grade.28 While the presented study recorded 10% of online education materials (n = 5) meeting this readability recommendation, this growth may be negligible given the three years or more since the Guan et al.25 publication. In addition, the average FRE measurement of Grave's disease is in concordance with previous literature in 2014 by Edmunds et al.26 which employed a similar screening methodology. In this study, the FRE score of Grave’s disease educational articles was found to qualify as “difficult to read” by FRE measurement. In fact, the current Grave’s diseases FRE of 37.81 was lower than what was found in the Edmund’s et al.26 study. This was likely because the current study used a larger sample (n = 50) of online education materials which were dedicated to Grave’s disease materials in comparison (n = 20). Regardless, this finding further compounded the need to attempt to simplify the readability of Grave’s disease literature. To the best of our knowledge, there was no dedicated literature on the readability of adrenal-related endocrine care, so the findings of this study were novel without a comparison. Moreover, the lack of adrenal-related online patient education materials which met the grade level readability recommendations raised priority in emphasized improvement in these materials.8,9

This study had multiple aspects which strengthens its findings. For example, the screening methodology accounted for 1,500 total online education materials and 10,500 readability quantification measurements creating the largest sample related endocrine care to date. The employment of seven scales minimized any potential measurement bias between scales. Secondly, this sample size had characteristically included material which were not formally scientifically indexed to limit variation in grade level readability as the audience of literature in PubMed or other scientific indexes may not be intended for the general audience.

However, this study was not without its limitations. The methodology did not account for utilization of other internet search query programs other than Google®. Google® comprised over 90% of the internet search query market share in the past year,51,52 so the methodology was believed to cover a valid portion of relevant online education materials. The methodology also implemented a plain text reformat of all included online education materials which this study failed to account for an illustration or digital materials which has been shown to aid in improving healthcare literacy as well as patient-physician discussions.51

In addition, the inclusion criteria focused only on online education materials which were written in English and not formally peer reviewed. Thus, the results of this study may not apply to online education material which was not written in English. However, the increased use of online language translation applications raised the potential to investigate if there are any discrepancies in readability amongst foreign language texts.54,56

Another potential concern was consideration with temporal changes in search engine trends and the presence of a potential “bubble effect”.57

Thyroid cancer had the highest FRE measurement at 47.95 (CI: 44.20 - 51.70), which would qualify as “difficult to read”. Likewise, hyperthyroidism had the lowest FRE measurement at 33.56 (CI: 29.15 - 37.97), which also would qualify as “difficult to read”. The average FRE of all other thyroid-related content was shown in Table 8.
Original literature on this form of selection bias was in the context of using internet search queries when screening literature for systematic reviews. This was to account for how search query programs may tailor search results specific to the user’s preferences. However, the ultimate purpose of a readability analysis is to focus on the online results of the general crowd, so various methods can be used to limit potential selection bias such as using a clear internet search cache or specifically establishing a period for which internet search queries are performed as seen in this study. Future directions to develop after this study may be to encompass a larger set of search terms (i.e., more than 30) and use search trend technology to collect the most relevant search queries by the general worldwide audience. In addition, a larger scope of endocrine care which includes pituitary-related online education material can validate current literature in the long term.

CONCLUSIONS

Healthcare literacy remains an important driving factor in the progression of a patient’s health condition and overall quality of life. Online education materials will continue to be a convenient source of information which can be used in the endocrinologist-patient relationship. However, the lifetime longitudinal care of patients with endocrine and metabolic diseases requires a greater awareness that the current climate of online educational materials do not meet readability recommendations for appropriate comprehension of the general audience.

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COMPREHENSION OF ONLINE PATIENT MATERIALS
continued.


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Keywords: diabetes mellitus, adrenal glands, thyroid, readability, patient education
Bilateral Upper Lobe Collapse Secondary to Vaping
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INTRODUCTION
Vaping and electronic (e-cigarette) use have been marketed as a “healthier” nicotine product as well as a smoking cessation tool.1,2 These products have been especially popular in younger populations, even as young as middle school-aged, and their use has been increasing over the past several years. There are many well-described pulmonary manifestations associated with e-cigarette or vaping product use-associated lung injury (EVALI), many of which are some degree of organizing pneumonia.3,4 This commonly is seen as ground glass opacities to focal consolidation in various locations on computed tomography (CT) scans. EVALI also has been associated with other organ system dysfunction including the cardiovascular (CV) and immune systems.5 Pneumothoraces and/or lung collapse were observed less commonly.6,7 When these findings were seen, they predominately were seen unilaterally.8 In this case, we described a patient with bilateral upper lobe collapse secondary to EVALI.

CASE REPORT
A 23-year-old male with past medical history of asthma and remote substance abuse presented with a new onset of seizures. Initial history was provided by Emergency Medical Services (EMS) and family members. The patient was lying in bed vaping and talking on the phone when he spontaneously began experiencing seizures. It was unknown how long the patient was convulsing prior to being found by his family. Midazolam was administered by EMS upon their arrival, which halted the seizures. When the patient arrived in the emergency department, he was tachycardic (134 BPM), tachypneic (RR 25), and hypoxic, requiring a non-rebreather mask to maintain appropriate oxygen saturations. He was afebrile.

Physical exam was pertinent for altered mental status and inability to follow commands, subcostal retractions, and diffuse rhonchi on respiratory auscultation. A rapid arterial blood gas showed respiratory acidosis. The patient was intubated for airway protection. Initial laboratory results showed a leukocytosis of 19.4 cells per microliter and a creatinine of 1.69 milligram per deciliters. Electrocardiogram showed sinus tachycardia and post intubation chest x-ray showed collapse of bilateral upper lobes (Figure 1). Computed tomography (CT) of the brain was unremarkable. CT chest confirmed bilateral upper lobe collapse (Figures 2 and 3).

The patient appeared to meet criteria for sepsis on admission. However, no infectious etiology was identified. This included blood cultures, cerebral spinal fluid cultures, and viral tests for human immunodeficiency virus, hepatitis, COVID-19, and influenza A and B. As a result, the patient was diagnosed with systemic inflammatory response syndrome (SIRS). The patient was extubated one day after intubation. Electroencephalogram was unremarkable for active seizures. The patient was treated with levetiracetam and was free of seizure activity for the remainder of his hospitalization. The patient’s renal function improved with intravenous fluids and the patient was discharged on day five of admission. Given the patient’s extensive workup and the unusual pattern of injury, it was concluded that his bilateral upper lobe collapse/atelectasis was secondary to vaping use.
DISCUSSION

EVALI is well-described with manifestations ranging from more benign with centrally located organizing pneumonia, to more severe with diffuse alveolar damage, which typically requires intensive care and ventilator support. Respiratory failure secondary to vaping/e-cigarette use can be difficult to determine early in the course, as the acute presentation can be similar to that of respiratory viral infections. This difficult diagnosis is especially pertinent in patients who require ventilator support and cannot provide a history of present illness, as seen in our patient. With increased vaping use being associated with more severe injuries and illness, physicians should have a high index of suspicion of vaping/e-cigarette use in younger patients who present with respiratory failure.

EVALI likely will continue to be a diagnosis of exclusion, and this was seen in our patient, who required an extensive workup. The exact mechanism of EVALI remains elusive, but is suspected to be related to the vast number of chemical agents found in the smoking products. This finding further emphasized the need for cessation and patient education.

CONCLUSIONS

In the presented case, an ostensibly rare complication of vaping use, bilateral upper lobe collapse/atelectasis, was described. Given our patient’s young age and lack of prior lung injury and comorbidities, the differential diagnosis remained broad, thus necessitating an extensive work-up. EVALI is a diagnosis of exclusion and requires a high degree of suspicion. With more younger patients using vaping products, it is likely that lung injuries will continue to be seen. Cessation and education of these products should be a continued discussion between patient and physician.

REFERENCES


Keywords: vaping, lung injury, e-cigarettes
Takotsubo Cardiomyopathy in a Vaccinated Patient with Severe COVID-19

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University of Nevada–Las Vegas, Kirk Kerkorian School of Medicine, Las Vegas, NV

INTRODUCTION

This case illustrated coronavirus disease-19 (COVID-19) induced interleukin-6 (IL-6) activation resulting in Takotsubo Cardiomyopathy (TCM) in a vaccinated patient. As noted by Kurowski et al., the pathogenesis of TCM includes a high inflammatory state leading to increased myocardial stress and eventual transient dysfunction. As such, the patient may present with cardiac chest pain mimicking acute coronary syndrome and signs of clinical heart failure. This complication should be part of the differential in patients who present with acute ST-elevation myocardial infarction (STEMI), with no cardiac risk factors and suspicion for severe inflammation. The RECOVERY Collaborative Group showed that the high inflammatory state seen in severe COVID-19 pneumonia can lead to major organ dysfunction, including TCM, and these patients also should be evaluated for immunomodulatory therapy targeting IL-6 as they may reduce mortality.

CASE REPORT

The patient was a 67-year-old female with a past medical history of chronic obstructive pulmonary disease, hypertension, and obesity who presented with 10 days of shortness of breath, fever, and fatigue. The patient received her second dose of the mRNA-1273 COVID-19 vaccine four days prior to admission, curiously while dyspneic, and when questioned further she was admitted by a family member who lives with her and subsequently tested positive for COVID during this period.

Physical exam was notable for irregular tachycardia and scattered rhonchi. Vitals were documented as blood pressure of 127/73 mmHg, heart rate of 127 beats/min, respiratory rate of 33 breaths/min, and oxygen saturation of 60% on room air improved to 92% on Bi-level Positive Airway Pressure. A computerized tomography chest scan with contrast was negative for an acute pulmonary embolism, but found bilateral interstitial opacities. Nasal swab polymerase chain reaction (PCR) testing was positive for COVID-19. Given this, she was admitted to the hospital for respiratory failure and management of her COVID. She was started on dexamethasone 10 mg once a day, with the intention of her infection and the negative coronary findings on angiogram, and avF with a high sensitivity troponin found to be greater than 3000 ng/L (admission high sensitivity troponin less than 60 ng/l). Notable laboratory anomalies included IL-6 levels of 54.9 pg/mL, D-dimer levels of 28.45 mcg/mL, and C-reactive protein levels of 91.4 mg/L. Given the acute presentation, ECG findings, and troponin elevation, the differential diagnosis included STEMI, TCM, and myocardial infarction (TIMI) 3 flow and a left ventriculogram with apical ballooning (Figure 1). A transthoracic echocardiogram with contrast showed ejection fraction 20-25%, normal left ventricular chamber size with basal wall hyperkinesis, and apical wall hypokinesis. The patient was admitted to the intensive care unit for her underlying COVID-19 pneumonia with findings consistent with TCM.

Figure 1. (A) Left ventriculogram consistent with apical ballooning. Angiogram showing good TIMI 3 flow in both the left (B) and right (C) coronary system.

Clinically, the patient continued to require high levels of oxygen via the ventilator with supportive care. Her inflammatory markers eventually trended down, as did her oxygen demand. A follow-up transthoracic echocardiogram showed return of normal cardiac function, ejection fraction of greater than 55%, and no regional wall abnormalities (Figure 2). Due to her lack of significant improvement and continued ventilator dependence, the multidisciplinary decision with the family was to have the patient undergo tracheostomy and percutaneous gastrostomy tube placement for long term convalescence. Given the improvement of her cardiomyopathy with the improvement of her infection and the negative coronary findings on angiogram, the diagnosis of Takotsubo cardiomypathy was believed to be most consistent.
DISCUSSION

Patients with Takotsubo cardiomyopathy classically present with typical chest pain and ECG findings of anterolateral ischemia. Of note, 1-2% of patients present with troponin positive suspected acute coronary syndrome or STEMI. This finding was postulated to be due to direct left ventricular myocardial injury and resultant troponin leak appearing as ST elevations in the anterolateral precordial leads. On ultrasound, the myocardial wall dyskinesis occurs over multiple coronary territories with no significant coronary stenosis seen on cardiac angiography further supporting a non-ischemic cardiomyopathy etiology.

Stress, either psychological or physical, was thought to be a major contributor to TCM, with an 89.9% predominance for female patients. A postulated theory includes increased levels of circulating catecholamines causing direct myocardial injury leading to classical left ventricular apical hypokinesis with basal hyperkinesis. One such stressor may be the extensive inflammatory disease that occurs during an acute COVID-19 infection. It was believed to be a response to IL-6 activation through either the classical or trans signaling pathways. IL-6 is produced transiently in response to infection and tissue injury, but prolonged inflammation can lead to continual synthesis leading to chronic inflammation and stress. A recent multicenter randomized control trial found a 4% reduction in all-cause mortality within the first 28 days for critically ill patients on tocilizumab with steroids against steroids alone. In our case, the presentation with angiography and echocardiogram correlates with TCM, but the patients’ comorbidities contraindicated tocilizumab.

Although novel therapies can be effective, the current strongest recommendation to prevent disease is vaccination. The two-part mRNA-1273 series provided viral protection with greater than 92% efficacy 14 days after the initial dose with greater than 94% efficacy two weeks after the second dose. Although there have been reported cases of post-vaccine TCM, the timing and exposure with positive PCR seen in this case points to natural viral transmission leading to TCM. Given the post-vaccination severe IL-6 mediated presentation by our patient, the importance of maintaining precautions prior to full vaccine series completion remains of utmost importance.

REFERENCES


Keywords: takotsubo cardiomyopathy, SARS-CoV-2 infections, myocardial infarction, treatment outcome, case study
Scleroderma as an Uncommon Cause of Pericardial Effusion


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INTRODUCTION

Autoimmune diseases are a rare but important cause of recurrent pericardial effusions, and patients with scleroderma often present with pericardial effusion as their initial symptom. Many patients with a rheumatologic condition go undiagnosed for years, as with the presented case. With recurrent effusion, one must investigate the cause to prevent worsening morbidity, as simple drainage will not prevent reaccumulation of the fluid. Recurrent effusion in an elderly patient regularly indicates a workup for possible malignancy, but if tissue and cytology are negative for malignant cells, then autoimmune diagnosis should be ruled out. During the patient’s hospital stay, she was found to have physical and laboratory findings consistent with scleroderma. Given her decompensated state after years of undiagnosed disease, little could be offered other than symptomatic relief. We stress the importance of considering rheumatologic causes of pericardial effusions, as early detection may change the clinical course of a patient significantly.

CASE REPORT

A 70-year-old female with recurrent pericardial and pleural effusions presented to the emergency department with bilateral lower extremity swelling. She recently was admitted for a similar presentation at an outside facility, treated with diuretics, and discharged. Notably, she had regular outpatient pulmonology appointments for recurrent pleural effusions with no known cause and negative malignancy workup.

On presentation, her temperature was 98.1°F, blood pressure 61/52 mmHg, heart rate 98 bpm, and respiratory rate 23 bpm saturating 95% on room air. Her physical exam was significant for cachexia with bitemporal wasting and bilateral elbow and distal interphalangeal joint edema without erythema. She exhibited jugular venous distension and distant heart sounds.

Initial lab findings were significant for mildly elevated B-type natriuretic peptide (450 pg/mL); troponins, creatinine, and lactic acid were within normal limits. An echocardiogram showed an ejection fraction > 55%, right ventricular systolic pressure > 60 mmHg, a moderate-sized pericardial effusion with right ventricular collapse during diastole, and mildly dilated right ventricle and bilateral atria (Figure 1).

Given her clinical deterioration with tamponade physiology, a decision was made to perform a fluoroscopy-guided pericardiocentesis. Fluid cytology and culture were negative, and cell count was significant for white blood cells with polymorphonuclear predominance (Table 1).

Given her clinical deterioration with tamponade physiology, a decision was made to perform a fluoroscopy-guided pericardiocentesis. Fluid cytology and culture were negative, and cell count was significant for white blood cells with polymorphonuclear predominance (Table 1). Given her negative cytology and recurrent effusions with joint edema, further workup resulted in a normal ESR, elevated CRP (36), positive ANA antibody with a homogenous staining pattern (1:80), and positive scleroderma antibody (Table 2).

DISCUSSION

Autoimmune diseases are rare, and it is common for rheumatologic conditions to be either misdiagnosed or undiagnosed. Up to 25% of patients with rheumatologic diseases were unable to receive a definitive diagnosis, while others were undiagnosed for an average of 5 to 10 years. The rheumatologic disorder diagnosed in this case study, scleroderma, has a prevalence of 135 million to 184 million cases in the U.S. The majority of patients are female, and those particularly with scleroderma present with a complication of pericardial effusion at an average age 52.2 ± 10.8 years.

Table 1. Laboratory analysis breakdown of contents in pericardial fluid.

<table>
<thead>
<tr>
<th>Component</th>
<th>Reference Range &amp; Units</th>
<th>Patient Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Blood Cell count</td>
<td>160 mm³</td>
<td></td>
</tr>
<tr>
<td>Red Blood Cell count</td>
<td>&lt; 2,000 mm³</td>
<td></td>
</tr>
<tr>
<td>Polymononuclear Neutrophils</td>
<td>58%*</td>
<td></td>
</tr>
<tr>
<td>Mononuclear cells</td>
<td>42%*</td>
<td></td>
</tr>
</tbody>
</table>

*Values provided for informational purposes only, as there is no generally accepted reference interval.

Table 2. Laboratory result breakdown of autoantibodies present in patient’s blood.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Reference Range &amp; Units</th>
<th>Patient Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear Antibody Screen</td>
<td>Negative &lt; 1:80 Borderline 1:80 Positive &gt; 1:80</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti-DNA Antibody, double strand</td>
<td>0-9 IU/ml Negative &lt; 5 Equivocal 5-9 Positive &gt; 9</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Jo-1 Antibody</td>
<td>0.0-0.9 AI</td>
<td>&lt; 0.2</td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>0.0-0.9 AI</td>
<td>&lt; 0.2</td>
</tr>
<tr>
<td>Scleroderma Antibody</td>
<td>0.0-0.9 AI</td>
<td>2.8</td>
</tr>
<tr>
<td>SSA Antibody</td>
<td>0.0-0.9 AI</td>
<td>&lt; 0.2</td>
</tr>
<tr>
<td>SSB Antibody</td>
<td>0.0-0.9 AI</td>
<td>&lt; 0.2</td>
</tr>
<tr>
<td>Anti-Smith Antibody</td>
<td>0.0-0.9 AI</td>
<td>&lt; 0.2</td>
</tr>
</tbody>
</table>
In scleroderma patients, pericardial effusions occur at a frequency of 17%, and pleural effusions occur less frequently at a rate of 7%. Cardiac involvement at presentation (pericardial effusion or cardiac tamponade) was shown to be either prior to or simultaneous with a diagnosis of scleroderma in 32.5% of cases. Cardiac symptoms of scleroderma were associated with an increase in mortality by 2.8 fold, with a large portion due to arrhythmias or severe heart failure.

Treatment options for pericardial effusion in scleroderma include medical management with steroids, non-steroidal anti-inflammatory drugs, colchicine, or surgical intervention through pericardiocentesis or pericardial window. The majority of cases may be treated with medical therapy, reserving surgical intervention for more severe cases. Patients with pulmonary hypertension or an effusion causing hemodynamic compromise are advised to be optimized medically and managed cautiously to prevent cardiovascular collapse, reserving surgical intervention in cases that are absolutely necessary.

With our patient’s advanced age, significant cachexia, and recurrent pleural effusions, clinical signs suggested the more common explanation of malignancy, and past encounters treated her accordingly. Her deviation from the typical age range of scleroderma and lack of other cardinal findings aside from her effusions did not fit the typical scleroderma picture, possibly resulting in misdiagnosis and a likely more severe presentation during our encounter.

Because autoimmune diseases are rare, it is often the last etiology pursued, if at all. Yet, knowing that a significant percentage of scleroderma patients initially present with pericardial and/or pleural effusions was essential, and our decision to seek less common explanations led to her definitive diagnosis. Although our patient and family elected hospice, if her etiology was found earlier, it may have reduced her long-term morbidity and a more promising outcome may have been reached. We stress the importance of considering rheumatologic causes of pericardial effusions, as early detection can change the clinical course of a patient significantly.

REFERENCES

Keywords: systemic scleroderma, pleural effusion, autoimmune diseases, case report
Mobile Health Clinics as a Healthcare Delivery Model to Address Community Disparities

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INTRODUCTION

The commentary by Rumalla et al.³ observed the socioeconomic levels and corresponding healthcare disparities between Wyandotte and Johnson counties, which encompass the Greater Kansas City area. A salient observation was the notably higher exposure to primary care providers and lower preventable hospital stays in Johnson County, which also had a greater median household income and educational training. Since that commentary, there have been a number of public health initiatives that have been updated to improve concurrent local health disparities.²⁻⁴ In particular, the Kansas City Community Health Improvement Plan (KC-CHIP) established numerous goals to improve public health infrastructure, which included educational funding in disinvested areas with lower property values for 2022-2027.⁴ Moreover, there have been notable trends seen in the most recent data extracted from KC HealthMatters⁵ (2015-2019) when compared to the 2014 extraction by Rumalla et al.¹ for the Wyandotte and Johnson counties (Table 1).²

In 2014, the median household income in Wyandotte County increased from $33,163 to $46,881.⁵ Likewise, the median household income in Johnson County increased from $75,139 in 2014 to $89,087. What makes the income growth more encouraging, however, is that the Wyandotte County growth is over $10,000 more than the calculated United States Consumer Price Index inflation between 2014 to 2019 ($80,855). The income growth in Johnson County was over $8,000 more than its inflation between 2014 to 2019 ($80,855).

The percentage of people aged 25 and older with a high school diploma or higher grew 0.3% in both counties (Wyandotte County: 78.9%; Johnson County: 96.0%).² However, the Wyandotte County growth rate can be of concern when considering that Wyandotte County has approximately 17% fewer people than Johnson County, therefore a greater increase would be desired to reduce healthcare disparity.

The number of primary care providers per 100,000 individuals has decreased 24.6% percent in Wyandotte County between 2014 and 2018, whereas this number has increased 19.2% in Johnson County.⁵ This slower improvement seemed to make a weaker correlation to what was noted by Han et al.⁷ which suggested income and resources for wealth were associated with educational success. From a primary care standpoint, a higher education attainment also was associated with higher measurements in health literacy, so the Wyandotte County measurements in health literacy were imperative to understand the socioeconomic climate.⁸⁻¹⁰

Moreover, poor health literacy was well established in literature to lead to increased hospital costs for the patient, as well as increased morbidity and mortality.¹¹⁻¹³ This issue further was compounded by the decrease in provider availability in Wyandotte County. This unfortunate decrease created a strain to the current network of available providers for patients in addition to the current healthcare infrastructure. This infrastructure included the concept of the healthcare safety net for first line emergency care in the form of emergency departments, emergency medical services providers (EMS), and public or free clinics.¹¹⁻¹³

A potential solution provided by Rumalla et al.¹ was student-run free health clinics. This healthcare delivery model has been well-established in literature to address several healthcare disparities, including health literacy, primary care screening, and education.¹⁴⁻¹⁸ In addition, the student-run free health clinics create valuable learning opportunities for its student volunteers.¹⁹⁻²⁰ However, the growing strain on the local health safety net also may require additional interventions. This intervention could be additional student-run free health clinics.²⁰ This article aimed to provide a community level solution which may provide another distinctive solution that could work complementary to student-run free health clinics.

Mobile Health Clinics

A Mobile Health Clinic (MHC) is another community level intervention which can reduce the growing healthcare safety net strain.¹¹ Similarly to student-run free health clinics, this intervention functions specifically as a delivery model for various medical services, including primary care and screening, preventative specialty care, and social interventions.²²⁻²⁴ However, the unique quality which MHCs have is their ability to serve as a satellite medical facility that can allow for access to a wider demographic by geography. In addition, MHCs further remove the potential healthcare barrier of transportation for those who do not have a reliable source, and increase the convenience of healthcare access for the population who may have a reliable source of transportation.²³⁻²⁵ The migratory characteristic carried by MHCs opens greater opportunities to establish patient rapport through a continued presence among communities which creates longitudinal care, and a foundation for greater provider trust by the patient.²⁰

MHCs, by concept, create an environment which improves health literacy for both the patient and provider.²²⁻²⁵ Specifically, a patient having access to healthcare resources can create natural learning opportunities for themselves to improve healthcare literacy. However, the provider also gains a firsthand experience into physically being in their patients’ community. This primary experience creates a greater sensory exposure which may not have been provided in the provider’s training or a standard health clinic by being in one geographic location.

The fiscal implications of MHCs may create an encouraging proposition for their use in the community. In a community health survey by Attipo-Dorcoo et al.²⁵, the types of healthcare services provided by 49 MHCs were recorded and an estimated mean cost range per patient visit was calculated to be lower than the standard costs for Medicare beneficiaries obtaining the same services at an institution. Community-level utilization of MHCs created a cost-savings environment in...
the form of reducing the number of avoidable emergency department visits.22,27

The current situation of MHCs in the state of Kansas is encouraging. According to the Mobile Health Map,27 a collaborative network of MHCs in the United States which pool data on reported services and operation demographics (i.e., intended communities, mailing addresses, etc.), there are nine MHCs reported in Kansas. In comparison to the bordering states, Kansas had more reported MHCs than Nebraska (n = 6) and Oklahoma (n = 4), but far less than Colorado (n = 16) and Missouri (n = 27). Furthermore, six MHCs provided primary care services, and one also provided mammography screening, and another provided disaster relief services.27 Based on the provided mailing address for each MHC, Johnson (n = 3), Shawnee (n = 3), Crawford (n = 1), Sedgwick (n = 1), and Saline (n = 1) provided MHCs. If an MHC will provide healthcare coverage to the county where it is located, then approximately 4% of the square area of Kansas is covered by at least one MHC. This implied that more MHC coverage, by county, could lead to more opportunities for individuals to receive healthcare services.

Additionally, these clinics rely on volunteers, including students, for day-to-day operative tasks like the student-run free health clinics discussed by Rumalla et al.23 This volunteer opportunity provides students supplemental clinical exposure and practice to their medical training and was vital in exposing students to diverse patient populations. Finally, while MHCs create an overall beneficial healthcare delivery model, they also are not without limitations. The cost saving previously described also required an initial investment, which may require avenues to obtain this startup funding.22,23,27 MHCs also must require carefully planned logistics and volunteers to provide equitable care for each location.23,27 Despite these limitations, there were over 900 MHCs reported on Mobile Health Maps.27

CONCLUSIONS

Overall, the journey toward equitable health care will continue to require a multifaceted approach towards its delivery of care. Community level interventions such as MHCs are a promising concept which had unique characteristics that may lessen the burden on the healthcare safety net. This migratory delivery model allowed for greater geographic coverage, improvements in health literacy for both the patient and provider, fiscal impact, and education initiatives. Therefore, further studies to grow the literature on the community effects by MHCs is needed.

Table 1. Temporal comparison of KC HealthMatters data.5

<table>
<thead>
<tr>
<th>Wyandotte County</th>
<th>Johnson County</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Household Income</strong></td>
<td><strong>People 25 and older with a High School diploma or higher</strong></td>
</tr>
<tr>
<td>$33,163</td>
<td>$46,881</td>
</tr>
<tr>
<td>$46,881</td>
<td>$75,139</td>
</tr>
</tbody>
</table>

*Most recent measurement period is 2018.

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REFERENCES

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MOBILE HEALTH CLINICS continued.

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