ORIGINAL RESEARCH

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Polypharmacy Frequency: The Relationship Between Polypharmacy and Mortality in COVID-19 (+) Older Adults

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Abstract

Objective: This study aims to determine the relationship between polypharmacy and Coronavirus disease-2019 (COVID-19) (+) related mortality.

Materials and Methods: All older adults >60 years old who had positive COVID-19 polymerase chain reaction tests were included in the study, designed retrospectively. Polypharmacy was defined as drug use of five or more.

Results: One hundred and ten people of >60 years old were included in the study. Fifty-nine (53.6%) of the participants were male and the mean age was 70.5+8.81. The prevalence of polypharmacy in patients diagnosed with COVID-19 infection was 31.8% (n=35). Eighty-two (78.8%) of participants had pneumonia. Mortality occurred in 24 (21.8%) of the participants. There was no relationship between polypharmacy and mortality (p=0.241). In multivariate analysis, older age was associated with mortality (odds ratio: 6.82 95% confidence interval: 2.46-18.91, p<0.001).

Conclusion: The prevalence of polypharmacy in individuals diagnosed with COVID-19 infection was like the literature. The most significant factors in death in people with COVID-19 infection were older age. There was no relationship between polypharmacy and mortality.

Keywords: Older age, COVID, polypharmacy, mortality, coronavirus

Introduction

The pandemic of Coronavirus disease-2019 (COVID-19), which started in China in December 2019, caused the death of 1.311.942 people, infecting about 54 million people worldwide by 15 November 2020 (1). COVID-19 infection can be asymptomatic-mild upper respiratory tract infection or it can present with pneumonia and, acute respiratory distress syndrome (2-5). In many studies on COVID-19, older age and comorbidity has been associated with poor outcomes (2,3,5-7). Results are worse in older adult individuals who need mechanical ventilation (3).

In Turkey, the first case was reported on 11 March 2020 - the first death was seen on 17 March 2020 (8). By 10 February 2021, total cases and deaths had reached 2.548.195 and 26.998 cases in Turkey, respectively (8).

With aging, the number of diseases increases; therefore, the number of drugs used by people increases (9). Polypharmacy is an acute geriatric syndrome (10). Polypharmacy incidence has been reported from 30% to 60% in older adults (10-12). The reason for such a difference in polypharmacy incidence is that there is no universal definition of polypharmacy (10). Some define it as drug use other than indication (12), while others define it with more drug use than a certain number of drugs (10,13). Polypharmacy has been associated with many clinical conditions such as falls, mortality, adverse drug events, impaired cognition, and frailty (10,11,14). Until now, many factors related to mortality have been revealed in patients with a diagnosis of COVID-19, but there are a limited number of studies evaluating them in terms of geriatric syndromes (3,6,15). In the studies performed, mortality with frailty was evaluated, and unlike expectedly, no relation with mortality in frail patients was

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shown (6,15). There are few studies of the relationship between polypharmacy and COVID-19 related mortality, and their results are conflicting (3,6).

This study aimed to clarify the relationship between COVID-19 and polypharmacy because the research results published so far are contradictory. This study aims to determine the prevalence of polypharmacy in patients diagnosed with COVID-19 (+), to investigate whether the presence of polypharmacy in patients with COVID-19 (+) has an impact on mortality, and to identify other causes of mortality in people diagnosed with COVID-19 (+).

Materials and Methods

All older adults >60 years old who had a positive COVID-19 polymerase chain reaction (PCR) test at Erciyes University Medical School Hospital were included in the study. Erciyes University Medical School Hospital was the reference hospital for the pandemic. This research had been designed retrospectively. For the retrospective design, we did not evaluate the comprehensive geriatric assessment and frailty status of patients.

The files of the participants included in the study were scanned retrospectively. Their socio-demographic characteristics (age, gender), comorbidities [e.g., chronic obstructive pulmonary disease, cancer, hypertension (HT), coronary artery disease, chronic kidney disease, and/or diabetes mellitus (DM)], the number of drugs, the types of drugs, the presence of pneumonia, the history of admission on intensive care unit (ICU), the history of mechanical ventilation and the presence of mortality were recorded.

COVID-19 was detected by real-time reverse transcriptase-PCR assay of samples collected by using nasopharyngeal swabs. Computed tomography (CT) was performed on all patients without contraindications (claustrophobia, etc.), who resulted in COVID-19 PCR positive. A specialist radiologist evaluated CT. Patients with infiltration on CT were considered to have COVID-19 pneumonia.

In this study, five or more drug use was defined as polypharmacy (10). When the patients admitted to the hospital, those who used five or more medications regularly for the last year were accepted as "polypharmacy". The drugs were recorded through the patients' reports during hospitalization and controlled from the medulla system (in Turkey). The drugs used by the patients were categorized as antihypertensive, antiaggregant, anticoagulant, antidepressant, antidiabetic (AD) drugs, inhaler drugs, antilipidemic drugs, immunosuppressant drugs, and proton pump inhibitors (PPIs).

This research was approved by the Erciyes University Ethics Committee (date: 10.06.2020, number: 2020/285). Consent was obtained from the participants or their relatives.

Statistics

Histogram, q-q plots are examined, and the Shapiro-Wilk's test was applied to assess the data normality. Levene test was used to test variance homogeneity. To compare the differences between groups, the Pearson chi-square test or Fisher's Exact test were applied for categorical variables to compare the differences between groups. Mann-Whitney U tests were applied for continuous variables. Binary logistic regression analysis models were built to investigate the effect of variables in estimating mortality in geriatric patients. Crude, age, and gender-adjusted, and multiple models were fitted separately. Significant variables at $p<0.25$ were included in numerous models, and backward elimination was performed to identify independent risk factors. Wald statistic was used as a model selection criterion. Hosmer-Lemeshow tests were used for the goodness of fit test. Odds ratios were calculated with 95% confidence intervals. All analyses were performed using TURCOSA (Turcosa Analytics Ltd. Co., www.turcosa.com.tr) statistical software. P-values less than 5% were considered as statistically significant.

Results

One hundred ten people of >60 years old were included in this research. Fifty-nine (53.6%) of the participants were male and the mean age was 70.5 (64.0-78.2, standard deviation 8.81). Ninety-five (86.4%) of the participants had comorbidities. The most common comorbidity was HT with 61.8% (n=68) patients, the second was DM with 28.2% (n=31) patients. Polypharmacy was recorded in 31.8% (n=35). The most widely used drugs were diuretics (hydroxychlorothiazide, spironolactone) (n=41, 37.3%), beta-blockers (n=34, 30.9%), acetyl-salicylic acid (ASA) (n=32, 29.1%), angiotensin receptor blockers (ARB) (n=31, 28.2%), calcium channel blockers (n=26, 23.6%), angiotensin-converting enzyme inhibitors (ACE-I) (n=24, 21.8%) and metformin (n=21, 19.1%). While a total of 78.8% (n=82) had COVID-19 pneumonia. Ten (9.1%) of 110 participants had a history of admission in ICU, and five (4.5%) had mechanical ventilation. Mortality occurred in 21.8% (n=24) of the participants. Table 1 shows the demographic and clinical characteristics of the participants according to mortality. The participants who had mortality were older (69 vs. 79.5, $p<0.001$). Moreover, the mortality rate was higher in hospitalized individuals (69.8% vs. 100%, $p=0.002$). Table 2 shows the relationship between drug groups and mortality. There was no relationship between any drug group and mortality. Thirteen (22.0%) of the patients with mortality were male and 21.6% (n=11) were female ($p=0.570$). Twelve (13.8%) of those with mortality were between the ages of 60-79 and 52.2% (n=12) were over 80 years old ($p<0.001$). While no mortality occurred in patients who were followed at home, mortality was observed in all hospitalized and followed up ($p=0.002$). Admission in ICU and history of mechanical ventilation were not associated with mortality ($p=0.08$ and

0.227, respectively), but the number of patients was very low for these parameters.

The Hosmer-Lemeshow test was applied for each final models resulted in X^2=0.371 p=0.831 for mortality. These results revealed the built multiple binary logistic regression model's appropriateness in predicting the clinical outcomes in geriatric patients. Table 3 shows the univariate, adjusted, and multiple logistic regression analysis results identifying the risk factors of mortality. In univariate analysis, we found that people with intubation history increased the mortality risk 48.6 times (odds ratio: 48.60 95% confidence interval 13.35-176.94, p<0.001). History of intubation was not included in the multivariate analysis since it would suppress all other multivariate analysis parameters. Gender, polypharmacy, and the presence of COVID pneumonia parameters do not affect mortality in univariate analysis. We found that age was the only parameter affecting mortality in univariate analysis. When an adjusted model was established considering the effects of age and gender, that the variables of polypharmacy and the presence of COVID pneumonia do not affect mortality. In our study, the only factor that affects mortality was age. Patients aged 80 and over had a mortality rate of 6.82 times higher than patients aged 60-79 (p<0.001). The same situation was similar in the multiple models.

Discussion

In the present study, the prevalence of polypharmacy in patients diagnosed with COVID-19 infection was 31.8%. Mortality occurred in 21.8% of the participants. There was no relationship between polypharmacy and mortality. The most important factor associated with mortality was older age.

Until now, quite a few studies have examined the relationship between polypharmacy and COVID-19. In one of them, De Smet et al. (6) reported a higher prevalence of polypharmacy than ours (64% vs. 31.8%), but the number of patients in this study was less than our study. Until now, there were very few publications on polypharmacy and COVID-19 related mortality. While no relationship was found between mortality and polypharmacy in one of these studies (6), another study found polypharmacy to increase the mortality risk (3). Polypharmacy has been shown to increase mortality in older adults in many meta-analyses (11,12). However, surprisingly, this study did not show an association between polypharmacy and mortality (41.7% vs. 29.1%, p=0.241). Therefore, some things that affect outcomes in COVID-19 infection may be thought to be different from prognostic factors (age, sex, polypharmacy, and comorbidities) described in other cases. More research is needed to clarify the relationship between polypharmacy and COVID-19.

Table 1. The characteristics of patients with COVID-19 (+) with or without mortality

Variables	Total n (%) n=110	Survivors n (%) n=86 (78.2)	Non-survivors n (%) n=24 (21.8)	p
Age	70.50 (64.0-78.2)	69.00 (63.75-76.00)	79.50 (71.00-87.00)	**<0.001**
Age 60-79 ≥80	 87 (79.1) 23 (20.9)	 75 (86.2) 11 (47.8)	 12 (13.8) 12 (52.2)	**<0.001**
Gender Male Female	 59 (53.6) 51 (46.4)	 46 (78.0) 40 (78.4)	 13 (22.0) 11 (21.6)	0.953
Comorbidity HT DM CAD COPD CKD Carcinoma	 68 (61.8) 31 (28.2) 28 (25.5) 17 (15.5) 4 (3.6) 5 (4.5)	 52 (60.50) 24 (27.90) 21 (24.40) 14 (16.30) 2 (2.30) 4 (4.7)	 16 (66.70) 7 (29.20) 7 (29.20) 3 (12.50) 2 (8.30) 1 (4.2)	 0.580 0.903 0.637 0.651 0.164
Number of comorbidity	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.572
Number of drugs	3.00 (1.00-5.20)	3.00 (1.00-5.00)	3.50 (2.00-6.00)	0.450
Polypharmacy	35 (31.80)	25 (29.10)	10 (41.70)	0.241
Presence of COVID pneumonia	82 (78.80)	67 (77.90)	15 (62.50)	0.126
Follow-up status Home Hospital	 26 (23.60) 84 (76.40)	 26 (30.20) 60 (69.80)	 0 (0.0) 24 (100)	**0.002**
Admission on ICU	34 (30.90)	10 (11.60)	24 (100)	**<0.001**
Mechanical ventilation	5 (4.50)	5 (5.80)	18 (75.00)	**<0.001**

CAD: Coronary artery disease, CKD: Chronic kidney diasease, COPD: Chronic obstructive pulmonary disease, COVID: Coronavirus, DM: Diabetes mellitus, HT: Hypertension, ICU: Intensive care unit, values are expressed as n (%) or median (1^{st}-3^{rd} quartiles). Adjusted p-values are calculated using Benjamini-Hochberg procedure and significant adjusted p-values are shown in bold

There were many studies in the literature that have examined various drug groups and the relationship of COVID-19. In some of these researches, the use of metformin (16,17), DPP4-I (16), ACE-I (18-20), ARB (18-20), statins (20,21) and chronic anticoagulants (22,23) was protective against COVID-19-related mortality. However, results in other studies were in the opposite direction. Kocayigit et al. (24), found no association between mortality and type of antihypertensive agents' use. In the study of Cheng et al. (25), no effect of metformin use on mortality was found. In research investigating the relationship between many drug groups and mortality in Iran (26), only statin group drugs decreased mortality. In contrast, non-steroidal anti-inflammatory drugs, ACE-I, and ARB use did not show any effect on death. In another study on diabetic COVID-19 patients (27), the use of AD agents (insulin, metformin, sulfonylurea, and DPP-4 inhibitors) did not have a protective effect on mortality. The factors that were effective in drugs to prevent mortality in those researches improve the immune response, reduce the inflammatory response, block renin-angiotensin-aldosterone system, and prevent the formation of thrombosis (17,19,21,22). Our study examined the relationship between nine different drug groups (antihypertensive, antiaggregant, anticoagulant, immunosuppressant, inhaler, antidepressant, antilipidemic and AD drugs, and PPI) and mortality, and we found no relationship (Table 2). Randomized controlled studies are needed to understand precisely what the effects of drugs on COVID-19 related mortality.

When the patients with mortality in COVID-19 patients were examined in the literature, it was seen that 20-80% of them were over 60 years old (2,4,28,29). In some research in Turkey (3,5), were like our research for over 60 years older patients (23.1% vs. 21.8%, 21.2% vs. 21.8%). When we divide it into groups by age, the mortality rates are similar to the literature and in Turkey (3,30,31). In our research, the mortality rate between the ages of 60-79 was 13.8%, and over 80 years old, was 52.2%, respectively. We found that the mortality risk increased approximately seven times in individuals aged 80 and over. As in our research, many studies have reported that older age was a risk factor in COVID-19 related deaths (3,6,7,15,24,28,29). Why is COVID-19 infection more mortal in older adults? Immunosenescence, or changes in the age-related immune system, primarily affects the adaptive immune system (32). Accordingly, intracellular pathogens are more frequent and/or severe infections (33). A decrease in T-cell and B-cell functions in relation to older age makes it challenging to limit viral replication (32). Both older age and increasing type 2 cytokine production impairs cell-mediated immune responses to infectious challenge (32). Also,

Table 2. Comparison types of drugs between mortality

Variables	Survivors n (%) n=86 (78.2)	Non-survivors n (%) n=24 (21.8)	p
Any antihypertensive drugs			
ACE-I	20 (23.30)	4 (16.70)	0.586
ARB	24 (27.90)	7 (29.20)	0.903
Beta blocers	23 (26.70)	11 (45.80)	0.085
Calcium channel blocers	17 (65.40)	9 (37.50)	0.101
Diuretics	32 (37.20)	9 (37.50)	0.979
Alfa blocers	1 (4.20)	1 (1.20)	0.390
Any antiaggregant drugs			
ASA	9 (37.50)	23 (26.70)	0.305
Clopidogrel	6 (25.00)	11 (12.80)	0.143
Ticagrelor	0 (0.0)	2 (2.30)	0.451
Any anticoagulant drugs			
Warfarin	1 (4.20)	1 (1.20)	0.475
Rivaroxaban	0 (0.0)	2 (2.30)	
Immunosuppressant drugs	0 (0.0)	3 (3.50)	0.474
Inhaler drugs	3 (12.50)	14 (16.30)	0.464
Antidepressant drugs	0 (0.0)	7 (8.10)	0.169
Antilipidemic drugs	5 (20.80)	15 (17.40)	0.453
Any antidiabetic drug(AD)s			
Biguanides	2 (8.30)	19 (22.10)	0.129
DPP-IV inhibitors	7 (29.20)	23 (26.70)	0.814
Other oral ADs	2 (8.30)	4 (4.70)	0.390
Insulin	5 (20.80)	11 (12.80)	0.323
Proton pump inhibitors	5 (20.80)	9 (10.50)	0.178

Blockers, ASA: Acetyl-salicylic acid, DPP: Dipeptidyl peptidase, values are expressed as n (%). Adjusted p-values are calculated using Benjamini-Hochberg procedure and significant adjusted p-values are shown in bold. ACE-I: Angiotensin-converting enzyme inhibitors, AD: Antidiabetic drug, ARB: Angiotensin receptor

Table 3. Univariate and multiple logistic regression analysis results in identifying the risk factors of mortality

	Crude model		Adjusted model		Multivariate model	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age, 60-79 ≥80	 6.82 (2.46-18.91) 1.00	 **<0.001** -	 - -	 - -	 6.82 (2.46-18.91) 1.00	 **<0.001** -
Gender Male Female	 0.97 (0.39-2.41) 1.00	 0.953 -	-	-	-	-
Polypharmacy (>5 drugs)	1.74 (0.68-4.42)	0.244	1.78 (0.65-4.93)	0.264	-	-
Presence of COVID pneumonia	0.47 (0.18-1.25)	0.130	0.48 (0.16-1.37)	0.169	-	-

CI: Confidence interval, COVID: Coronavirus, OR: Odds ratio. Adjusted models are controlled for age and gender

susceptibility to thrombosis and thromboembolism increases with older age (32,34-36). Systemic inflammation is a condition that enhances procoagulant effects (34,35). Many studies published to date have found abnormalities in coagulation-related values in laboratory tests, and these abnormalities were associated with mortality in COVID-19 patients (2,4,37). For these reasons, COVID-19 infection is more severe and mortal in older adults.

Study Limitations

There are some limitations to this study. The most important limitation was single-centered and of small sample size of the present study. Also, people with negative tests but radiologically with COVID-19 pneumonia were not included in this study. Therefore, the findings in this study, unfortunately, do not reflect all individuals with COVID-19 pneumonia. The government determines hospitalization and treatment algorithms for people diagnosed with COVID-19. So, there must be some selective bias. One of the limitations was that the presence of drug-drug interaction had not been studied. There was no information about the laboratory parameters and treatment modalities of the participants. Therefore, the effects of the treatments received by individuals on mortality have not been studied. Further studies are still needed.

Conclusion

In summary, the prevalence of polypharmacy in individuals diagnosed with COVID-19 infection is like the literature. The most significant effect on mortality in people with COVID-19 infection is older age. Further studies with more participants are needed to clarify the relationship between COVID-19 infection and polypharmacy.

Ethics

Ethics Committee Approval: This study is approved by the Erciyes University Ethics Committee (date: 10.06.2020, number: 2020/285).

Informed Consent: Consent was obtained from the participants or their relatives.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.Ş.D., S.A., Design: N.Ş.D., S.A., Data Collection or Processing: N.Ş.D., S.A., T.S., Z.T., Analysis or Interpretation: N.Ş.D., G.E.Z., S.A., Literature Search: N.Ş.D., S.A., Writing: N.Ş.D., S.A.

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