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Original Article

Outcome of COVID-19 Positive Patients with type 2 Diabetes and Polypharmacy: an Examination of a Tertiary Hospital Cohort

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ABSTRACT

Background: COVID-19-positive patients are at increased risk of adverse clinical outcomes, with type 2 diabetes cohorts at substantially higher risk compared to the general population. The additional role of diabetic and non-diabetic polypharmacy in these patients' clinical course has remained unexamined. In this study we have comprehensively examined the role of polypharmacy in the determination of mortality outcomes in patients with COVID-19 clinical syndrome.

Methods: We retrospectively examined case notes and electronic records of N = 497 patients with type 2 diabetes and COVID-19 infection. We ascertained the number of medications each patient was taking and used this to categorize the study cohort into diabetic [n = 246] (5 or more diabetic medications), and non-diabetic polypharmacy [n = 251] (5 or more non-diabetic medications). The primary outcome was the need for intensive care admission between the two groups.

Results: In patients with "non-diabetic polypharmacy" (>5 medications), advancing age, and higher HBA1c levels, were associated with increased risk of Intensive care admission (OR 1.06 [CI 1.03-1.07], P = <0001), (OR 1.01 [CI 1.01- 1.20], P 0.017), respectively. Patients taking 5 or more non-diabetic medications had an increased likelihood of admission into the intensive care unit compared to those on lower medication thresholds (OR = 1.7; CI = 1.1 to 1.3; p-value = <0.0006).

Conclusion: In an inpatient cohort of type 2 diabetic patients with COVID-19, non-diabetic polypharmacy was associated with a multiplicative risk of intensive care admissions. This will necessitate the need for periodic medication reviews in these cohorts of patients to mitigate these potential risks and improve clinical outcomes.

Key words: COVID-19, polypharmacy, Diabetes Mellitus, adverse drug reactions

INTRODUCTION

Despite the uptake of COVID-19 vaccination programs around the world as part of the comprehensive attempt at addressing its rising morbidity and mortality, the evolution of new variants of the virus has continued to be a source of ongoing concerns. [1,2] These include the B.1.617.2 (delta) and B.1.1.529 omicron (Pango lineage B.1.1.529)

variants. [1] During the initial period of the pandemic and subsequently, clinical uncertainty with the most optimal therapeutic strategy meant that patients were exposed to a dynamic guideline-sanctioned cocktail of drugs and putative agents. [3] To date, dexamethasone, [4] and suppressive antiviral therapy (Paxlovid) [5,6] have thus far stood out as the only strategies proven by randomized controlled clinical trials to positively alter the morbidity and mortality matrices associated with the disease. [4,70] Nevertheless, the residual uncertainty regarding organ-specific interventions (such as treatment of associated pneumonia and other infective syndromes accompanying COVID-19) meant that these patients still end up with a drug cocktail as part of their treatment regimen. This increasing pill burden (polypharmacy) comes with a multiplicative risk of drug-drug, drug-food, as well as pharmacogenetic interactions. These, of course, are in addition to the inevitable risk of adverse drug reactions (ADR). [8] Despite uncertainty regarding the exact medication thresholds that define what constitutes polypharmacy in specific organ morbidities (heart failure, chronic liver disease, etc.), its deleterious effect on overall patients' morbidity and mortality has never been in doubt. [9 10] In the general population, a patient's intake of 5 or more medications is classified as major polypharmacy [10]; whilst minor polypharmacy refers to medication thresholds less than 5. Earlier studies, including the report from a Dutch cohort, have already reported a high prevalence of polypharmacy amongst patients with type 2 diabetes mellitus (T2DM). [12,13] These patients are at a disproportionately higher risk of COVID-19-related adverse outcomes, including Intensive care admissions and death. [14] Factors predisposing to this are legion, but they include the duration of diabetes and the level of glycemic control, amongst others. [14,15] The role of medication burden (as exemplified by polypharmacy) in all of this has remained unexamined. For example, are there differences in outcomes between COVID-19 patients taking different thresholds of diabetic medications? (Less than 3, or greater than 5, etc.); or do outcomes of patients on diabetic polypharmacy differ from those with polypharmacy in general (here referred to as "non-diabetic" polypharmacy)?

In this study, we have explored the pattern and the clinical phenotype of diabetic and non-diabetic polypharmacy in patients with T2DM and COVID-19, as well as its impact on the risks of potentially adverse clinical outcomes such as intensive care unit (ITU) admissions.

MATERIALS AND METHODS

Study design and setting

This retrospective study examined case notes and electronic records of a randomly selected cohort of patients (*n*=2014) with type 2 Diabetes Mellitus and a confirmed diagnosis of COVID-19 presenting to the Hamad General Hospital, Doha, Qatar between March 2020 and December 2020. This is a tertiary healthcare facility with a capacity of 600 beds, catering to patients referred from other primary and secondary healthcare centers in the state of Qatar. The number of medications each patient was cumulatively prescribed was abstracted from an online prescription platform (Cerner®). Disordered glycemic control often accompanies COVID-19 infection, consequently, we did not censure the timing of medications included in the patient's total medication list, as some of these patients had either insulin or other diabetic drugs added to their medication list upon diagnosis of COVID-19 to optimize their glycemic control. Other variables abstracted include age (then categorized into 18-25, 26-35, 36-45, 46-55, 56-65, 66-75 years), gender, self-declared ethnicity, eGFR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum interleukin 6 (IL-6), serum ferritin, serum D-dimer, length of hospital stay, and intensive care unit (ITU) admission. The primary outcome was admission to the ITU. We chose ITU admission as a surrogate marker of COVID-19 severity as it has previously been reported as a reliable index of COVID-19 interventions (including various pharmaco- and immunotherapies) (15). The admission criteria for intensive care admission were usually patient-specific, but broadly, patients within our study cohort were admitted for ventilatory support. These include non-invasive ventilation, mechanical ventilation, or sequential ventilation for patients who needed it. We chose potential confounders (based on their biological plausibility as well as recent reports of their association with the risk of adverse outcomes in these cohorts of patients) from a list generated by direct acyclic graphs (DAG) utilizing the Dagitty software (16).

Study population

Type 2 diabetic patients with COVID-19 infection confirmed by nasopharyngeal swab polymerase chain reaction (PCR). We included all diabetic patients regardless of the duration of diagnosis.

Inclusion and exclusion criteria

The inclusion criteria were

- New or preexisting diagnoses of type 2 diabetes
- COVID-19 infection.
- On index medication for at least 4 months

The exclusion criteria include the Unavailability of data

Sample size

Given the prevalence of COVID-19 in Qatar of 16.2%, we estimate that a sample size of 2014 is likely to give us about 80% power to detect the differential effect of diabetic polypharmacy on COVID-19 clinical outcomes.

Case ascertainment and definitions.

In this study,

- "Diabetic" polypharmacy was defined as the intake of 5 or more diabetic medications (including insulin). A different cohort of type 2 diabetic patients taking 5 or more non-diabetic medications (and fewer than 5 diabetic medications) was classified as having "non-diabetic" polypharmacy.
- A positive COVID-19 case refers to patients with positive PCR from a nasopharyngeal swab.

Statistical analyses

Continuous variables were compared and summarized as means (±SD) or medians (interquartile range [IQR]) using ANOVA and Kruskal-Wallis, depending on the distribution as appropriate. Differences in the distribution of categorical variables were determined by Chi-squared tests. Correlation coefficients were derived to ascertain the correlation between study variables. Bivariate analyses were utilized to determine the relationship between study variables and risk of intensive care admissions. Multivariate regression models were generated to determine factors associated with the risk of ITU admission in type 2 diabetic patients who are COVID-19 positive. These include specific outcome comparisons between "major" and "minor" polypharmacy, as well as "diabetic" and "non-diabetic" polypharmacy. All analyses were carried out with Stata Statistical Software (Stata Corp. 2019. Release 16. College Station, TX: Stata Corp LLC)

Ethical approval

The protocol and various documentation for this study, including consent to access the records of participants in the study, were reviewed and approved by the independent review board of the medical research center (**MRC-01-21-167**).

RESULTS

The baseline characteristics of the study population are shown in **Table 1**. Amongst an inpatient cohort of *N* = 2014 T2DM patients with COVID-19, the proportion of the study population with "diabetic" and "non-diabetic" polypharmacy was (N = 246, and N = 251, respectively). The mean age of the study cohort was 54.8 [SD ±10] years, with a male population of 65.3%. The median number of comorbidities was 4 (interquartile range 2-8). About 94.5% of the study population was on an insulin-based regimen. The distribution of drug classes amongst patients with "diabetic" and "non-diabetic polypharmacy" is shown in Tables 4 and 5.

Table 1: Baseline characteristics of different clinical phenotypes of "diabetic" and "non-diabetic polypharmacy

Variable	Total population	Diabetic polypharmacy (*N* = 246)	Non-diabetic polypharmacy (*N* = 251)
Age (years) /Mean (SD)	54.8 (± 10.8)	55.32 (± 10.7)	54.7 (± 10.6)
Male Gender /N (%)	1316 (65.3)	153 (62.2)	1163 (65.8)
Arab Ethnicity /N (%)	1044 (51.8)	150 (61.0)	894 (50.6)
Years DM/Median (IQR)	3.9 (1.7, 4.6)	4 (1.8, 4.5)	3.9 (1.7, 4.7)
Serum IL6/ Median (IQR)	30.5 (8, 107)	18 (12,38)	56 (8,110)
Serum D-dimer Median (IQR)	0.57 (0.36, 1.09)	0.56 (0.37, 1.05)	0.57 (0.36, 1.1)

Table 2: Multivariate analyses and adjusted odds ratios for the effect of Diabetic Polypharmacy on intensive care (ITU) admissions

Variable	Diabetic polypharmacy			Non-diabetic polypharmacy		
	Odds ratio	Confidence interval	*p*-value	Odds ratio	Confidence interval	*p*-value
Age /Mean (SD)	1.02	0.98-1.07	0.392	1.06	1.03-1.07	<0.001
Years DM/ Median (IQR)	0.98	0.78- 1.24	0.9	0.89	0.82- 0.962	0.004
Serum IL6/ Median (IQR)	0.98	0.930- 1.03	0.50	1.00	0.99- 1.02	0.190
Serum D-dimer/ Median (IQR)	1.23	0.72- 2.19	0.41	1.20	1.07- 1.34	0.001
Serum Ferritin/ Median (IQR)	0.99	0.99-1.00	0.676	0.99	0.99-0.1.0	0.662
eGFR/ Median (IQR)	0.97	0.92- 1.03	0.340	0.94	0.92-0.96	<0.001
HBA1c/ Median (IQR)	1.11	0.56- 1.12	0.204	1.10	1.01- 1.20	0.017

Table 3: Cummulative effect of age category on ITU admissions in type 2 Diabetic patients with COVID-19 and established markers of endothelial dysfunction (raised D-dimer levels)

Age category	D-dimer Median (IQR)	OR (CI)©	*p-value*
18-25 Years (n =3)	0.22 (0.22, 0.34)	-	-
26-35 Years (n = 8)	0.19 (0.26, 0.42)	-	-
36-45 Years (n = 15)	0.3 (0.35, 0.56)	1.96 (0.58-6.58)	0.276
46-55 Years (n =98)	0.31 (0.43, 0.69)	1.07 (0.92-1.25)	0.364
56-65 Years (n =111)	0.35 (0.54, 1.03)	1.11 (1.00-1.23)	0.047
66-75 Years (n =81)	0.35 (0.55, 1.16)	1.47 (1.02-2.13)	0.041

Diabetic vs. Non-Diabetic Polypharmacy

The adjusted ORs (AORs) and their 95% CIs derived from multivariable logistic regression models are given in **Table 2**. The presence of non-diabetic polypharmacy (5 or more non-diabetic medications) was associated with increased risk of Intensive care admission (Odds ratio = 1.7 [Confidence interval (CI) 1.1 to 1.3]; p = 0.0006). In patients with non-diabetic polypharmacy, advancing age, higher HBA1c levels, and every additional year since diagnosis of diabetes were associated with increased risk of Intensive care admission (OR 1.06 [CI 1.03-1.07], P = <0001), (OR 1.01 [CI 1.01- 1.20]), (OR 0.9 [0.82-0.962]) respectively. We found out of the three markers of endothelial injury evaluated (viz. serum Ferritin, IL-6, and D-dimer), only rising serum D-dimer levels were associated with a doubling of the risk of Intensive care monitoring in patients with nondiabetic polypharmacy but with an uncertain point estimate (OR 1.07 [CI 1.07- 1.34]. Of note, none of the tested covariates were predictive of ITU admissions in patients with diabetic polypharmacy (5 or more diabetic medications, including insulin).

The cumulative effect of age on the risk of intensive therapy unit (ITU) admissions

We additionally explored the differential effect of age categories on the risk of ITU admissions in the setting of COVID-19 in patients with non-diabetic polypharmacy and evidence of "endotheliopathy" as evidenced by raised D-dimer. Patients with raised D-dimer levels within the age categories (56-65 and 66-75 years) were associated with increased risk of ITU admissions (OR = 1.11 [CI 1.00-1.23], p = 0.041), (OR = 1.47 [CI 1.02-2.13], p = 0.041) respectively. See **Table 3**

Table 4. Drug classes among patients with non-diabetic polypharmacy phenotypes

Drug classes	Types of drug analogues
Angiotensin-converting enzyme (ACE) inhibitors	Ramipril, Lisinopril, Perindopril, Enalapril
Angiotensin II receptor blockers (ARBs)	Losartan, Irbesartan, Telmisartan, Valsartan
Mineralocorticoid receptor antagonist	Spironolactone
Statins	Atorvastatin, Pravastatin, Simvastatin
NSAIDS	Ibuprofen, Naproxen
Anticonvulsants	Gabapentin, Pregabalin, Sodium valproate, Levetiracetam
Diuretics	Furosemide, Torsemide, Bumetanide
Antidepressants	Duloxetine, amitriptyline

Table 5. Diabetic drug classes amongst patients with Diabetic polypharmacy phenotypes

Drug classes	Types of drug analogues
Sulfonylureas	Glyburide, Gliclazide
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Sitagliptin, Linagliptin
Thiazolidinediones	Pioglitazone
GLP-1 analogues (Incretin mimetics)	Dulaglutide, Liraglutide, Exenatide
Biguanides	Metformin
Prandial glucose regulators	Repaglinide
SGLT2 inhibitors	Empagliflozin, Dapagliflozin
Insulin	Various preparations (Glargine, Levemir, Actrapid, Novorapid)

DISCUSSION

To our knowledge, this study's examination of different polypharmacy phenotypes and their impact on COVID-19 ITU-related admissions represents the first comprehensive exploration of the association between this rising therapeutic morbidity and adverse outcomes in these cohorts of patients. We found a 2-fold increase in the risk of ITU admissions amongst patients taking more than 5 non-diabetic medications compared to those on lower medication thresholds or taking 5 or more diabetic drugs. This will call for increased vigilance and the institution of mitigation strategies to address this additional risk factor in these patient cohorts who are already at increased risk of ITU admissions. Our findings are consistent with recent reports that have investigated polypharmacy and multimorbidity in COVID-19 patients (3). The most notable of these is the report from an examination of a population cohort by Sirois et al. [18]. Out of 32,476 COVID-19-positive patients evaluated by this study, 10,350 (32%) of them were hospitalized with a mortality rate of 13% (n = 4146). Rising medication counts in this study were associated with higher relative risks of hospitalizations [relative risk 1.11 (95% CI 1.04 to 1.19)] for those using 5–9 medications, compared to 1.62 (95% CI 1.51 to 1.75) for those using 20+ medications. This outcome was also consistent with the risk of death as a factor of increasing medication counts (OR 1.13, 95% [CI 0.99 to 1.30] for those using 5–9 medications; to OR 1.97, 95% [CI 1.70 to 2.27] for patient cohorts on ≥20 medications). Earlier reports in this area during the pandemic were limited to a specific examination of the additive effect of increasing medication number and multimorbidity on the risk of obtaining a positive COVID-19 PCR test [3]. As has been evident throughout the pandemic, and even with subsequent new variants (such as the omicron variant), a significant proportion of individuals with a positive COVID-19 test are either asymptomatic or have mild disease with no need for hospitalization or intensive care admission. Having a quantitative measure of the risk of progression from positivity to the need for ITU monitoring is therefore useful. Several of these measures have been investigated, with some at various stages of validation. [12] Polypharmacy, unfortunately, has evolved as an inevitable consequence of the management of a rising number of morbidities, not the least of which are patients with T2DM. Several studies have nearly doubled the number of patients who are at a higher baseline risk of COVID-19 deterioration compared to other patient cohorts. [18,19] Whilst the exact reason for this remains a matter of pathophysiological debate, some of the factors so far studied include inherent susceptibility and level of glycemic control, amongst others. [19] But the role of medication burden as an attributable risk of ITU admission has not been examined until now.

Our finding of differences in outcomes between patients with non-diabetic polypharmacy compared to those with diabetic polypharmacy is interesting. The lack of demonstrable adverse outcomes with the latter (by way of ITU admissions) will reinforce the earlier findings from previous reports on the role of optimal glycemic control in mitigating COVID-19 adverse clinical outcomes. [20] Indeed, this observation is further reinforced by our finding of the near doubling of ITU admission

risk for every unit increment in the HBA1c level. Conversely, it could be argued that the type of diabetic drug utilized in attaining this optimal control was more important than the absolute number of drugs used; this, especially with the recent reports alluding to the salutary role of" insulin sensitizers "(such as metformin and Pioglitazone) on morbidity and mortality outcomes in patients with COVID-19 positive. [18,21,22]

Our finding of increased risk of ITU admissions for each additional year since the diagnosis of T2DM for both diabetic and non-diabetic polypharmacy may denote the duration of T2DM as a surrogate marker of associated T2DM complications (including micro and macrovascular diseases). These complications have been well established to be a factor of the length of T2DM, amongst other factors. The presence of these overt and sub-clinical complications, therefore, perhaps plays an additional yet-to-be-determined role in promoting endothelial dysfunction, a key driver of deterioration and the need for supportive intensive monitoring in patients with COVID-19 infection. [17] Studies in the general population have shown a rising risk of medication burden with advancing age [18, 31], partly accounting for the rising prevalence of polypharmacy across various clinical risks and morbidities.

We observed that a sizable proportion of our study population was on insulin (94.5%). The impact of tight glycemic control on favorable COVID-19 outcomes has been exhaustively explored elsewhere. [14,25–28] But we suspect the higher insulin prescription amongst our patient cohorts may be consequent upon the desire by treating physicians to optimize glycemic control; a therapeutic strategy recognized in the early phases of the pandemic and suggested to reduce adverse COVID-19 clinical outcomes. [32]. We hypothesize from our observation and other published reports that diabetic medications on their own are probably protective against COVID-19 and its adverse outcomes, and it may therefore be a significant contributor to our observation of good outcomes in patients with diabetic polypharmacy (intake of 5 or more diabetic drugs). We investigated the 3 commonly reported markers of endothelial injury (Serum Ferritin, IL-6, and D-dimer) in COVID-19 patient cohorts to ascertain the exact relationship between their diagnostic thresholds and the presence of any of the polypharmacy phenotypes investigated. Only rising serum D-dimer levels were found to be associated with a near doubling of the risk of ITU admissions in patients with non-diabetic polypharmacy (but with an uncertain point estimate (OR 1.20 [CI 1.07- 1.34], p= 0.001). Despite this observation, all 3 markers report varying patterns of "endotheliopathy," which has been extensively reported to be the harbinger of both ITU admissions and death in this cohort of patients. [29–31]

Strengths and limitations

The novelty of our report lies in being the first attempt at investigating the relationship between various phenotypes of polypharmacy in T2DM with COVID-19 clinical syndrome and adverse outcomes. Our findings both reinforced earlier observations in this area, but also reported several potential hypothesis-generating observations that will assist in the design of future studies in this area.

Our use of a retrospective data scheme meant that we had to deal with missing values as well as other issues encountered with retrospective study designs. But notwithstanding that, the consistency of our final point estimates across key report observations meant that this limitation is unlikely to affect any potential inference from our report.

CONCLUSION

In a population of type 2 diabetic patients with COVID-19 infection, non-diabetic polypharmacy in the setting of advancing age and rising HBA1c levels was associated with multiplicative risks of adverse clinical outcomes such as intensive care admission. This will necessitate the need for periodic medication reviews in these cohorts of patients to mitigate these potential risks and improve clinical outcomes.

AUTHORS' CONTRIBUTION

Each author has made a substantial contribution to the present work in one or more areas, including conception, study design, conduct, data collection, analysis, and interpretation. All authors have given final approval of the version to be published, agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

None.

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