JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Routine hemoglobin-A1c screening is required before the next pandemic to reduce morbidity and in-hospital costs

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Abstract

Introduction: Glycosylated hemoglobin (HbA1c) levels are routinely used in secondary and tertiary care centers for monitoring diabetes patients. However, since it is an expensive test, it is not routinely tested in primary care or used as a screening test. This study aimed to examine the relationship between HbA1c levels and in-hospital costs in hospitalized patients during the pandemic period to draw attention to the issue and to be prepared for future pandemics.

Methodology: The design of the study was retrospective and cross-sectional. The study was conducted in a tertiary hospital between March and December 2020. Independent variables, including HbA1c levels, comorbidities, age, and gender; and dependent variables including in-hospital costs, prolonged hospital stay (≥ 14 days), and 30-day mortality; were statistically analyzed.

Results: Overall, 517 patients were included in the study, and 96 of them had high HbA1c levels (HbA1c ≥ 7). The in-hospital costs were significantly correlated with HbA1c ≥ 7 as continuous variables, and HbA1c ≥ 7 was a better indicator of in-hospital costs compared to the diagnosis of diabetes. Patients with HbA1c ≥ 7 also had prolonged hospital stays and higher mortality rates, in addition to high in-hospital costs.

Conclusions: Routine testing of HbA1c levels might be cost-effective and should be performed at primary healthcare facilities.

Key words: COVID-19; HbA1c; morbidity; in-hospital costs; pandemic.

J Infect Dev Ctries 2025; 19(9):1330-1335. doi:10.3855/jidc.20233

(Received 16 April 2024 – Accepted 13 April 2025)

Introduction

Coronavirus disease 2019 (COVID-19) continues to place a significant financial strain on the economies of many countries due to treatment costs, in addition to the death and morbidity that it causes [1]. In the past two years, many clinical trials were launched, and many treatments were administered to patients, with the expectation of relieving the patients of the COVID-19 symptoms and the virus. Vaccine and drug development projects had to take up the lion's share of the scientific research funding.

Prior to the availability of the COVID-19 vaccines, the impact of the pandemic was so severe that even oxygen supplies were running low in several hospitals, and patients were facing challenges due to limited supply and rapidly rising costs [2]. While the global economy has been negatively affected by the pandemic, longer hospital stays and the requirement for intensive care are still major contributors to the rising in-hospital costs, as the pandemic is still not fully under control [3]. It is known that the presence of comorbid diseases, including diabetes, is a significant factor determining outcomes in patients hospitalized due to COVID-19 pneumonia [4].

Glycosylated hemoglobin (HbA1c) is used as a marker in diabetic patients for both diagnosis and disease monitoring [5]. HbA1 indicates the average glucose level over the last 2 to 3 months and is directly affected by blood glucose levels [5].

There is a growing body of research highlighting the rising prevalence of diabetes globally; however, much of the existing data focus primarily on diagnosis rates in developed nations. In contrast, the underdiagnosed rate of diabetes in developing countries remains particularly alarming, yet significantly underreported. This gap in knowledge is critical, as many individuals suffering from undiagnosed diabetes are unable to access timely treatment. Consequently, the economic burden of untreated diabetes increases hospital costs due to complications that could have been averted with early intervention. Addressing this disparity is essential for understanding the true impact

of diabetes on healthcare systems in developing regions, where resources are already limited and must be efficiently allocated to mitigate long-term costs associated with late diagnoses.

According to studies conducted during the pandemic period, elevated HbA1c increase the risk of mortality among COVID-19 patients [6,7]. However, investigations on the effects of prolonged hospitalization, the likelihood of developing complications, and the link between HbA1c and other morbidities have produced conflicting results [6,7]. Furthermore, the role of HbA1c as an indicator of hospital costs remains ambiguous, highlighting a significant gap in our understanding. This uncertainty underscores the necessity for more comprehensive investigations to determine how HbA1c levels correlate with healthcare expenses, especially in the context of diabetes management during and after the pandemic.

This study aimed to investigate whether the high HbA1c levels influenced in-hospital costs and prolonged hospitalization during the pandemic period in order to draw attention to the need for diabetes screening and to be prepared for future pandemics.

Methodology

Study design

This study was designed as a cross-sectional, single-center, retrospective study. The study population included COVID-19 pneumonia patients hospitalized in a tertiary university hospital between March and December 2020.

The inclusion criteria were laboratory confirmed COVID-19 pneumonia and age >18 years. Two different researchers performed the data extraction and subjects with missing or inconsistent data regarding hospital costs, length of hospitalization, presence of complications, comorbidities, or HbA1c levels, were excluded from the analyses (Figure 1). The independent variables were HbA1c levels, comorbidities, age, and gender. The dependent variables were in-hospital costs, prolonged hospital stay (≥ 14 days), 30-day mortality, and requirement of high-flow oxygen (HFO) or admission to the intensive care unit (ICU).

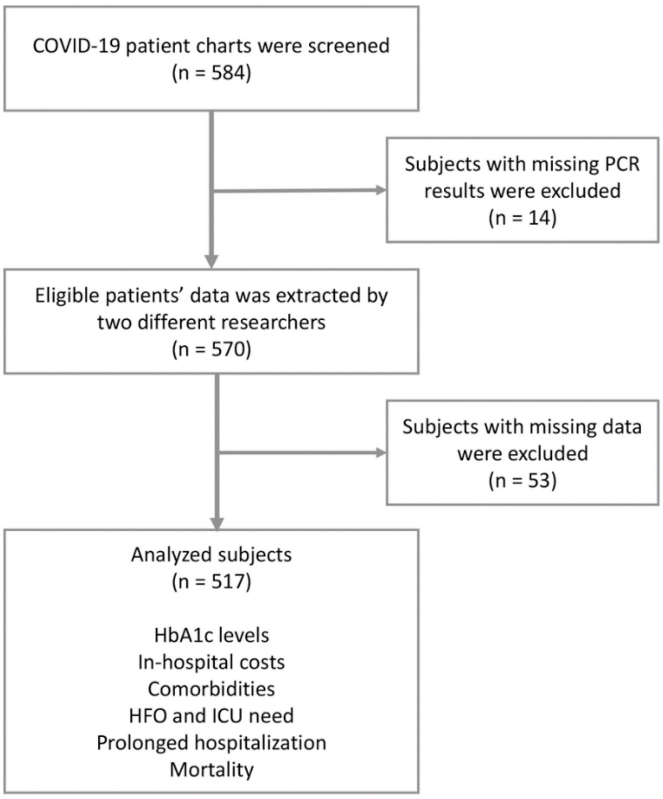
Methods of measurements

Nasopharyngeal swabs were collected from patients and analyzed using real time polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) quantification and diagnosis of COVID-19. Data was extracted from the hospital medulla system (electronic data management system) by two independent researchers and compared for consistency before proceeding to further analysis.

HbA1c levels were measured from venous blood samples of patients on the morning after the day of their hospitalizations, and measured using a Variant II Hemoglobin Testing System (BIO-RAD, Hercules, CA, USA) instrument with high-performance liquid chromatography (HPLC). HbA1c levels ≥ 7% were used when comparing to categorical comorbidities, according to the recommendation of the American Diabetes Association [8].

In-hospital costs were obtained from the hospital's computing department with the permission of the hospital administration and ethical approval was obtained from the university's ethical board. The costs included medications, disposable equipment, daily bed costs, and companion's daily cost. Comorbidities were recorded according to the patients' hospital records and medications. Hypertension (HT), diabetes mellitus (DM), chronic kidney disease (CKD), cancer, chronic obstructive pulmonary disease (COPD), or any disease requiring immune suppressive treatment were considered as comorbid diseases.

Figure 1. Flowchart presenting the selection of study population.



COVID-19: coronavirus disease 2019; PCR: polymerase chain reaction; HFO: high flow oxygen; ICU: intensive care unit.

Data analysis

Descriptive statistics were presented as median (min–max) for numeric variables, including HbA1c, hospital costs, and age. Categorical variables, including gender, comorbidity, HFO, non-invasive ventilation (NIV), ICU admission, prolonged hospital stays, and mortality, were presented as frequencies. Pearson correlation and linear regression analysis were used to evaluate the relation between HbA1c levels and in-hospital costs, unpaired t-test was used to determine differences between the continuous variables, and Fisher's exact tests were used to compare percentages between the groups.

In order to specifically test the regression assumptions in the analyses, tests for normality (using the Shapiro-Wilk test) were conducted to assess the distribution of numeric variables, including HbA1c and hospital costs. If any assumptions were violated, they were addressed accordingly by employing appropriate statistical techniques, including transformations or non-parametric alternatives, where necessary.

Prism 9 (GraphPad Software, LCC) [9] was used to perform statistical analyses and p value < 0.05 was considered statistically significant.

Results

Demographics and hospital costs

Overall, 517 individuals were included in the study. The median age was 55 (19–93) years, 56% were male, 69% had at least 1 comorbid disease, and the mean HbA1c level was 5.7% (Table 1). The median cost was 6,200 Turkish Liras (TL), and the total cost was 57 million TL (408,000 USD) for the 517 patients that were included.

Correlation between HbA1c and in-hospital costs

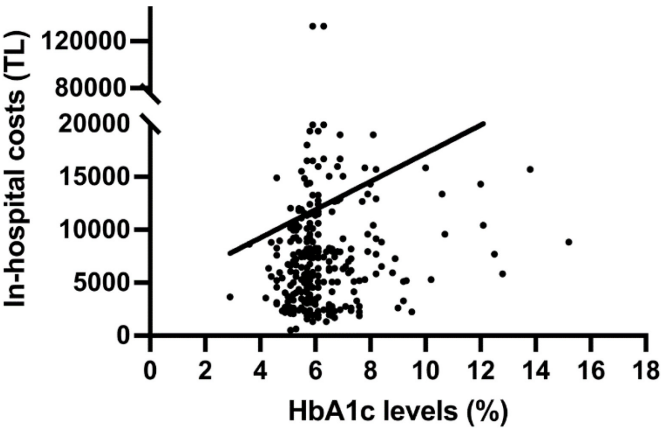
Correlation and linear regression analyses were performed to evaluate the relationship between HbA1c levels and in-hospital costs, and the results indicated a significant positive correlation between these two parameters (r = 0.1411, R^2 = 0.01990, p = 0.0105; Figure 2).

Table 1. Baseline characteristics of the study population.

Patients (n)	517
Age in years (median, min–max)	55 (19–93)
Male gender (n, %)	292 (56%)
HbA1c (median, min–max)	5.7 (2.9–15.3)
Patients with at least 1 comorbidity (n, %)	359 (69%)
Prolonged hospital stay (≥ 14 days)	83 (16%)
Need for HFO (n, %)	73 (14%)
ICU admission (n, %)	55 (10%)
Mortality (30 days) (n, %)	59 (11%)
In-hospital costs in Turkish Lira (median, min–max)	6200 (200–146000)

HFO: high flow oxygen therapy; ICU: intensive care unit.

Figure 2. Linear regression of HbA1c levels and in-hospital costs.



Y = 1330*X + 39, p = 0.0105. (r = 0.1411, R2 = 0.01990). TL: Turkish Lira.

Comparison of HbA1c ≥ 7 and DM indicators of in-hospital costs

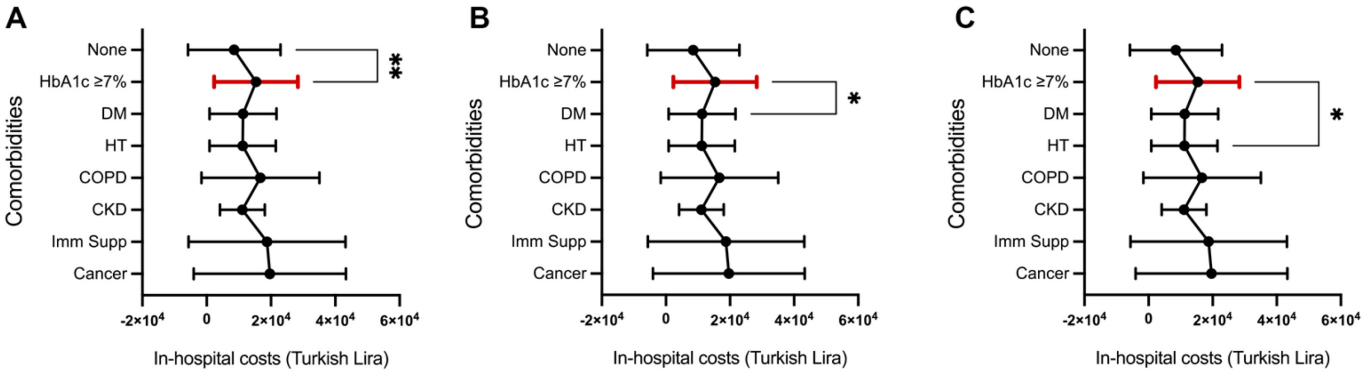
After noting the effect of HbA1c on in-hospital costs, the HbA1c values of ≥ 7 (considered critical [8]) were compared with other comorbidities in terms of their impact on hospital costs. The comorbid diseases included DM, HT, COPD, CKD, cancer, and immune suppressive treatment. When the demographic parameters were analyzed, a female dominancy was noted in the HbA1c ≥ 7 group (Table 2). As expected, COVID-19 patients with no comorbid disease were younger, compared to the others, and very few of them had HbA1c ≥ 7 (Table 2). Interestingly, only 48 (42%)

Table 2. Demographic characteristics of the patients in the comorbid groups.

	N	Age in years (median, min–max)	Male Gender (n, %)	HbA1c ≥ 7 (n, %)
No comorbid disease	158	41 (20–83)	95 (60%)	3 (1%)
DM	114	65 (35–88)	65 (57%)	48 (42%)
HT	158	66 (38–88)	69 (43%)	40 (25%)
COPD	29	66 (39–88)	17 (58%)	4 (13%)
CKD	30	68 (33–90)	18 (60%)	6 (20%)
Immune Suppression	46	58 (19–83)	23 (50%)	4 (8%)
Cancer	54	62 (19–89)	27 (50%)	8 (14%)
HbA1c ≥ 7	96	62 (44–81)	29 (30%)	96 (100%)

DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.

Figure 3. Bar diagrams show in-hospital cost comparison between HbA1c ≥ 7 group and the listed groups in y axes. A, No comorbidities group (p = 0.0036); B, DM group (p = 0.0362); C, HT group (p = 0.0228).



The HbA1c ≥ 7 group had significantly increased costs compared to the no-comorbidity group (None) (p = 0.0036). DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; Imm supp: immunity suppressed.

patients diagnosed with DM had HbA1c ≥ 7, whereas the total number of patients with HbA1c ≥ 7 was 96; indicating that 50% of the patients were not diagnosed with DM.

When comparing the in-hospital costs, HbA1c ≥ 7 was significantly associated with higher costs, than the no-comorbidity, DM, and HT groups (Figure 3). Other comorbidity groups, including cancer, COPD, immune suppressive, and CKD, had similar in-hospital costs with the HbA1c ≥ 7 group.

Association of prolonged hospitals stays and higher mortality rates with HbA1c ≥ 7

The study group was divided into two based on their HbA1c levels to compare the effects of high HbA1c levels on prolonged hospital stay and mortality, in addition to in-hospital costs. Based on Fisher's exact test analyses, patients with HbA1c ≥ 7 had significantly higher mortality and prolonged hospital stay (Table 3).

Discussion

The results of this study demonstrate that HbA1c levels influence COVID-19 related in-hospital costs. The in-hospital costs of patients were positively correlated with HbA1c levels, and patients with HbA1c ≥ 7 had prolonged hospital stays, high mortality, and higher costs; than patients with DM and HT.

The key factors that help prevent or delay the consequences of DM include maintaining a healthy body weight; engaging in regular physical activity; avoiding tobacco use; and consuming a well-balanced, nutrient-rich diet. In addition, correct medications, consistent screening, and management of complications can aid in the treatment of DM; and either delay or avoid the emergence of problems. During the pandemic, many members of the society, whether they had been diagnosed with diabetes or not, had been confined to their homes and bound to inactivity [10–12]. Additionally, people were also subjected to unmanaged and irregular nourishment at home. Therefore, it may not be possible to determine whether the HbA1c increase observed in this study is a consequence of the pandemic, or a diagnosis/discovery of an existing DM. Since the increased HbA1c levels are associated with the increased blood glucose levels over the previous 2 to 3 months [5], the proportion of the study group which included patients in the first 9 months of the pandemic, may have represented the population that was least affected by the in-house-confinement issues [12]. A study in England conducted on a similar time-range as this study, estimated that between March and December of 2020, there were about 60,000 people with delayed or undiagnosed diabetes [13].

There are also studies that evaluated the potential effect of the COVID-19 virus on HbA1c levels. One study suggested that the increase in HbA1c levels at the early stage of COVID-19 may be inaccurate because of

Table 3. Comparison of prolonged hospital stay and mortality ratio between normal HbA1c and high HbA1c groups.

	HbA1c < 7	HbA1c ≥ 7	Significance
N	421	96	
Prolonged hospital stays (>14 days) (n, %)	48 (11%)	28 (29%)	$p < 0.0001$
Mortality at day 30 (n, %)	18 (6%)	22 (23%)	$p < 0.0001$

the impact of SARS-CoV-2 on the movement of hemoglobin and/or the identification of highly glycosylated S-proteins on the surface of the SARS-CoV-2 virus. Therefore, the authors recommended to re-evaluate the level of HbA1c in patients who did not have high blood sugar levels, but had HbA1c > 6.0, after recovery from the active phase of the disease [14]. Another study, focusing on the dynamics of HbA1c levels in COVID-19 survivors, indicated that there was a significant decrease in HbA1c levels in most patients, including those with pre-existing diabetes, at both 6–8 weeks and 52 weeks after hospital discharge. Despite the overall decrease, the study suggested that SARS-CoV-2 may have a diabetogenic effect. This was based on the observation that some patients without pre-existing DM developed DM or impaired glucose tolerance during the follow-up period [15,16].

High HbA1c levels indicate uncontrolled DM and are linked to poor nutrition and health inequalities caused by low socioeconomic status [10,17]. According to the 6th Diabetes Atlas of the International Diabetes Federation (IDF), it is estimated that in 2035 Turkey will be among the top 10 countries with the highest diabetes population in the world [18]. This study demonstrated that 50% of the high HbA1c level patients did not have a prior diagnosis for DM, although they received treatment for COVID-19 in a tertiary hospital. These patients did not receive primary care, and their DM status was unknown, but they received treatment in a tertiary care facility because they had severe COVID-19, which imposed a greater economic burden. Therefore, it is important to increase awareness on DM, and adopt screening protocols to overcome future burden of the uncontrolled disease.

Studies that focused on COVID-19-related hospital costs due to DM indicated that uncontrolled DM led to increased hospital costs [18]. During the first wave of COVID-19, the estimated cost per hospital admission in Europe ranged from EUR 25,018 for people with good glycemic control to EUR 57,244 for people with poor glycemic control. The reason for this difference was explained by the fact that people with poor glycemic control were more likely to need intensive care, ventilator support, and longer hospital stay. The estimated cost per hospital admission for people without diabetes was EUR 16,993. The total cost for secondary care for COVID-19 in Europe was estimated to be EUR 13.9 billion. Treating people with diabetes would cost 23.5% of the total amount [19]. In Turkey, treatment costs of the citizens are covered by the government through the social security system, and therefore hospitals bills, including physician salaries are relatively inexpensive than in other European countries. In this study, the median in-hospital cost was approximately EUR 885 and the maximum cost was approximately EUR 20,000 (1 Turkish Lira = 7 Euro in 2020). The in-hospital costs in this study did not include the salaries of healthcare workers and physicians, or any expenses related to heat, electricity etc.

This study had several limitations. First, the study was conducted in a single tertiary hospital, which may not represent the entire community. Second, it was a cross-sectional study and therefore the total number of participants was limited. Finally, the reasons of increased costs and the impact on overall costs were excluded from the research due to insufficient data, which was a result of the retrospective design of the study.

The impact of high glucose and HbA1c levels on mortality of COVID-19 patients has been demonstrated in previous studies. A recent meta-analysis analyzed the data of 222 COVID-19 patients with mild and severe disease, and the results indicated that severe COVID-19 patients had higher blood glucose levels, but the HbA1c levels were only slightly increased in the same group [20]. Soon after this study was completed, two meta-analyses were published in mid-2021. One of these studies revealed that elevated HbA1c levels as a continuous variable was associated with increased risk of mortality or worsening of the disease [6], but the second one concluded the opposite [7]. The results of this study support the former study with a significant increase in the mortality and the risk of prolonged hospital stay. The difference between the studies may be attributed to the number of subjects and the population differences; however, careful monitoring of HbA1c levels, health education, and screening the risk groups are highly recommended.

Conclusions

HbA1c has the potential to prevent morbidity during pandemics when routinely included in healthcare screenings. Therefore, HbA1c should be considered for routine testing in the primary care system, to prevent morbidity and mortality, and to reduce in-hospital costs during future pandemics.

Acknowledgements

The authors thank the ATS Methods in Epidemiologic, Clinical and Operations Research (MECOR) Program Faculty for contributing to the manuscript. A part of this work was supported by the Cukurova University Scientific Research Council (BAP) grant TSA_2020_12947.

Ethical considerations

This study was initiated after obtaining approval from the university's Scientific Ethical Board (2021/109_22).

Authors' contributions

YS, study concept and design, manuscript draft; BC, EA, MSD, data acquisition; YS, AC, OB, EG, FK, data interpretation; EO and SK, critical revision of manuscript.

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Conflict of interest

No conflict of interest is declared.

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