No association of Gaucher Disease with COVID-19-related outcomes: a nationwide cohort study

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Abstract

Background
It is well documented that patients with chronic metabolic diseases such as diabetes and obesity are adversely affected by the Covid 19 pandemic. However, when the subject is rare metabolic diseases, there is not enough data in the literature.

Aim
To investigate course of COVID-19 among patients with Gaucher disease (GD), the most common lysosomal storage disease.

Methods
Based on the National Health System data, a retrospective cohort of patients with confirmed (PCR positive) COVID-19 infection (n=149,618) was investigated. The adverse outcomes between patients with GD (n=39) and those without GD (n=149,579) were compared in crude and propensity score matched (PSM) groups. The outcomes were hospitalization, the composite of intensive care unit (ICU) admission and/or mechanical ventilation and mortality.

Results
The patients with GD were significantly older and had a higher frequency of hypertension, T2DM, dyslipidemia, asthma or COPD, chronic kidney disease, coronary artery disease, heart failure, and cancer. Although hospitalization rates in Gaucher patients were found to be higher in crude analyzes, the PSM models (model 1, age- and gender-matched; model 2, matched for age, gender, hypertension, T2DM, and cancer) revealed no difference for the outcomes between patients with GD and the general population. According to multivariate regression analyses, having a diagnosis of GD was not a significant predictor for hospitalization ($p = 0.241$), ICU admission/mechanical ventilation ($p = 0.403$) or mortality ($p = 0.231$).

Conclusion
According to our national data, SARS-CoV-2 infection in patients with GD does not have a more severe course than the normal population.

Keywords
Gaucher; Coronavirus; COVID-19; SARS-CoV-2; Mortality; National; Turkey.

1. Introduction

Gaucher disease (GD) is the most common lysosomal storage disease globally, with an estimated incidence of 1:20,000 - 1:100,000.[1] Due to the deficiency of glucocerebrosidase, a lysosomal enzyme in the disease, glucocerebroside and some glycolipids accumulate in lysosomes within macrophages. These accumulations reach 20 to 100 times the normal level in tissues such as the spleen, bone marrow, liver, and bone, and as a result, various clinical findings due to organ dysfunction occur.[2]

It is well-documented that the presence of chronic diseases negatively affects the prognosis of COVID-19.[3] In the early COVID-19 pandemic, the rare disease population has been demonstrated to be negatively influenced in terms of service and resource utilization and physical and mental well-being.[4] Recently, anxiety and depression were reported at a higher prevalence among patients with a rare disease than in the general population.[5] A more recent study showed that hospital mortality due to COVID-19 was enormously increased these patients.[6] The same study also reported a higher inhospital mortality due to non-COVID-19 reasons when compared with the pre-pandemic numbers. Although a worse prognosis of COVID-19 is predictable in genetically inherited rare diseases such as GD, yet there is not sufficient information in the literature.[7]

This study aimed to investigate the course of COVID-19 among patients with GD with reference to the general population.

2. Materials & Methods

2.1. Study design and participants

A retrospective cohort study was carried out using the central database of the Turkish Ministry of Health. The design and procedures in the study are in accordance with the declaration of Helsinki and the study protocol was approved by the Ministry of Health Ethical Board (95741342-020/27112019).

A total of 149,671 COVID-19 diagnoses between March 11 and May 30, 2020, were evaluated. All subjects were PCR confirmed COVID-19 cases. Using the ICD-10 codes, 39 patients with GD were identified.

2.2. Data collection

Age, gender, smoking status, education, comorbid diseases, body mass index (BMI), chest computerized tomography (CT) on admission, certain medications (renin-angiotensin system [RAS] blocker, statin, and acetylsalicylic acid), and laboratory parameters were retrieved using the ICD-10 codes.

Among the comorbidities, hypertension (HT), type 2 diabetes mellitus (T2DM), dyslipidemia, obesity, asthma/chronic obstructive pulmonary disease (COPD), chronic kidney disease, coronary artery disease, heart failure and cancer were recorded. The laboratory values

including glucose level at the time of diagnosis, low-density lipoprotein cholesterol (LDL-cholesterol), estimated glomerular filtration rate (e-GFR calculated by CKD-EPI formulation), aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), lactate dehydrogenase, ferritin, lymphopenia and albumin levels were analyzed.

All blood tests were performed in hospital laboratories certificated by the Turkish Ministry of Health. Test results that were available within the last 10 days before the diagnosis of COVID-19 were included.

2.3. Definitions

The diagnosis of GD, hypertension, T2DM, dyslipidemia, obesity, asthma/COPD, chronic kidney disease, coronary artery disease, heart failure, and cancer was based on relevant International Classification of Diseases System-Tenth Revision (ICD-10) codes. Obesity was defined as BMI ≥ 30 kg/m^2.

2.4. Study Outcomes

The study outcomes were mortality, hospitalization, and admission to the intensive care unit (ICU) and/or mechanical ventilation due to COVID-19.

2.5. Statistical analyses

All data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows 25.0 (SPSS Inc. 111 Chicago, IL). Numerical variables were expressed as mean ± standard deviation (SD) or medians and interquartile range (IQR) and categorical variables as counts (n) and percentages (%). Normality of distribution was assessed using Kolmogorov–Smirnov or Shapiro-Wilk test. Differences between the groups were assessed using the Chi-square test for categorical variables and Student's t-test or Mann–Whitney U test for numerical variables.

Multivariate logistic regression analysis was performed to study the independent predictors of hospitalization, ICU admission/mechanical ventilation, and mortality. To ensure the consistency of the analyzes, similar crude and adjusted comparisons were performed in age-, gender- and comorbidity-matched case-control models. Statistical significance was set at two-sided $p \leq 0.05$.

3. Results

Of the 149,671 COVID-19 diagnoses, 39 patients were previously diagnosed with GD (2.6/10,000). The comparison of demographic and clinical characteristics of patients with and without GD are presented in Table 1. Patients with GD were significantly older and had a higher frequency of hypertension, T2DM, dyslipidemia, asthma or COPD, chronic kidney disease, coronary artery disease, heart failure, and cancer. The rates of certain medications such as RAS blocker, statin, and acetylsalicylic acid were also higher among patients with GD. Lung CT and laboratory findings were similar between patients with and without GD. However, mean e-GFR in GD patients was lower than those without GD.

The rate of hospitalization in GD patients was higher than in the general population in crude analysis (Table 1). However, the propensity score matching (PSM) model 1 (age- and gender-matched) and PSM model 2 (model 1 plus matched for hypertension, T2DM, and cancer) showed no difference in the rate of hospitalization and other outcomes between the GD patients and the general population (Table 2 and Table 3).

Multivariate regression analyses showed advanced age, chronic kidney disease, heart failure, CT findings consistent with COVID-19 and lymphopenia were the common associates of all three endpoints. In addition, male gender, presence of diabetes, and presence of cancer were associated with mortality. Similarly, male gender and presence of diabetes were associated with a higher ICU admission rate, and presence of dyslipidemia and coronary artery disease was associated with a higher hospitalization rate ($p < 0.005$ for all). On the other hand, having a diagnosis of GD was not a significant predictor for hospitalization ($p = 0.241$), ICU admission/mechanical ventilation ($p = 0.403$) or mortality ($p = 0.231$) (Figure 1).

The Kaplan-Meier curves of 30-day mortality were not significantly different between patients with and without GD ($p = 0.838$) (Figure 2)

4. Discussion

This study showed that diagnosis of GD alone does not independently contribute to a higher risk of hospitalization, the need for ICU admission and/or mechanical ventilation or mortality than other community members in the COVID-19 pandemic.

Advanced age and comorbid diseases such as obesity, diabetes, and hypertension negatively affect the COVID-19 prognosis.[8–11] In this context, COVID-19 could be expected to show a more serious course among patients with rare genetically transmitted diseases, due to both the underlying immune dysregulation and the accompanying comorbid diseases.[12] However, the data so far have shown that Gaucher patients were infected with SARS-CoV-2 at a similar rate (or even at lower rates according to some studies) to other individuals in the community.[13–18] In this regard, a study from the United States reported that the rates of patients with COVID-19 (10 of 151 adult patients with GD) were similar to other individuals in the community and that having a diagnosis of GD, the type of treatment or GBA1 genotype were not associated with symptomatic disease or PCR test positivity.[13] In addition, no COVID-19-related death was reported in any GD patient in these series.[13] In a screened cohort of 550 patients with GD from Israel, only one patient was found infected with SARS-CoV-2, and the patient survived without any complications following the 14-day quarantine period.[17] No proven COVID-19 was detected in the GD series reported from Italy and Morocco.[16,18] While these studies showed a similar or lower incidence of SARS-CoV-2 infection among GD patients when compared with the general population, they were not abl to present sufficient information about the outcome of GD patients with COVID-19. To our knowledge, only one mortality case of COVID-19 has been reported so far.[15] However, the 79-year-old Gaucher patient also had severe dementia and renal failure, and therefore, the mortality could not be attributed to GD alone. Nonetheless, all the studies emphasized that GD patients may experience problems in accessing their treatment during the COVID-19 pandemic and show deterioration of enzyme levels and other laboratory tests. On the other hand, data on the outcomes of GD patients with COVID-19 are very limited. Thus, current is one of few

comprehensive GD report to provide the outcome data of patients with Gaucher disease having a PCR confirmed COVID-19 diagnosis.

We observed Gaucher patients were older and had a higher comorbidity burden in crude analyses (Table 1), however, except for hospitalization, there was no difference in study outcomes between GD and the general population. Increased hospitalization rate in patients with GD is likely linked to increased age and comorbidity burden. Concerning the hospitalization outcome, in addition to the higher comorbidity burden, a previous diagnosis of GD alone might have caused a tendency towards hospitalization to practice a closer follow-up. In the comparison analyzes of the PSM models that were performed to eliminate age and comorbid factors that may affect the study outcomes, no difference was observed in all three outcomes between the two groups. In addition, GD was not a significant predictor in the multivariate regression analyses performed to explore the predictors of all three study outcomes. The 30-day survival curves were also similar to the general population. These findings support the hypothesis that "Gaucher's disease does not pose an additional risk for COVID-19", which has been mentioned in other studies.[13,14,17]

In the pathogenesis of COVID 19, the role of excessive inflammatory response is as important as direct viral damage.[19] Chronic inflammation, immune dysregulation, and enhanced activation of the coagulation and fibrinolytic systems are involved in the pathophysiology of GD. Besides, patients with GD have high levels of angiotensin-converting enzyme . In addition, respiratory problems are frequently observed in lysosomal storage diseases due to infiltrates accumulating in the pulmonary system.[20] These pathogenetic mechanisms might leave patients with GD vulnerable to COVID-19, as well as to poorer prognosis. However, studies

have shown that the SARS-CoV-2 virus can use some lysosomal pathways to escape from infected cells. The virus causes enzyme inactivity by deacidifying lysosomal degradation enzymes in infected cells, thus protecting them from intracellular clearance.[21] In a study that measured the burden of proinflammatory cytokines, a minimal increase in proinflammatory cytokines was found in infected GD patients, even among the symptomatic patients.[14] Hence, it was speculated that the accumulated glycosphingolipids promote immune tolerance rather than inflammation when exposed to COVID-19. Disrupted immune response may explain the question of why the majority of COVID-19 infected Gaucher patients in studies were asymptomatic. On the other hand, asymptomatic COVID-19 should not be underestimated in patients with GD.

Asymptomatic infections can have negative impacts on clinical progress in patients with GD, because their access to healthcare services is suspended during the quarantine. In the study of Andrade-Campos et al., it was reported that while there was no disruption in the treatment of those who received oral treatment during the pandemic process, one-fourth of those who received infusion treatment in the hospital could not receive at least one dose of infusion.[15] In a case report from Turkey, interruption of ERT in a patient with GD led to long-term deterioration of laboratory findings (such as decreased level of hemoglobin and platelets).[22] The fear of being infected by an asymptomatic carrier health worker or the hospital environment (62.9%) and the inaccessibility due to the reorganization of the infusion centers during the pandemic (37%) were identified as the most common obstacles for patients to have their infusions.[16] Although we do not have clear information about how and to what extent Gaucher patients are affected by the Covid process, it is known that proinflammatory cytokines (IL 4, 6, 13 and MIP1a) increase in Gaucher patients who do not receive treatment.[15]

This increase in inflammation may cause Gaucher patients to have a worse prognosis during the Covid period. This potential risk can be reduced by providing uninterrupted treatment modalities such as home replacement therapies, the widespread use of oral therapy agents, and more organized health service delivery plans.

Repurposing of drugs with other indications to treat COVID-19 is a newer approach, as very few treatment options are available. The iminosugar miglustat is a well-characterized drug for the treatment of rare genetic lysosome storage diseases, such as GD, and has also been described to be active against a variety of enveloped viruses. In an in vitro study, miglustat acted at the post-entry level and led to a marked decrease of viral proteins and the release of infectious viruses.[23] The mechanism may be the inhibitory activity towards α-glucosidases that are involved in the early stages of glycoprotein processing in the endoplasmic reticulum, leading to a marked decrease of the viral Spike protein. One explanation of a mild or asymptomatic course of COVID-19 in GD patients in the current study may be the potential antiviral action of the drugs used in the treatment of GD.

Some theoretical concerns about the use of hydroxychloroquine, one of the treatment agents recommended in treating COVID-19 in the early period of the pandemic, should be acknowledged. It was hypothesized that hydroxychloroquine may cause deterioration in autophagy functions in Gaucher patients.[24] In Turkey, particularly in the first year of the pandemic, hydroxychloroquine treatment was ordered in every COVID-19 positive case due to the domestic healthcare program. The fact that no significant complications were observed in our study population who used hydroxychloroquine may partly answer this concern.

There are some limitations to this study. Some of the clinical and laboratory data, such as the type of GD, duration of disease, history of splenectomy, and the type of treatment received for GD were not available in the dataset. We were not able to obtain data about disease severity and drug claims by the individual patients since the personal information in the database is secure and all data we have obtained were anonymized. The major strength of the study was that it was the most comprehensive GD report in the literature reporting the outcomes of a total of 39 COVID-19 positive cases. The inclusion of patients with confirmed PCR tests for COVID-19 and comparison analyses with well-matched PSM groups were the other strengths of our study.

5. Conclusion

This study from the Turkish nationwide COVID-19 database showed patients with GD were not at an increased risk of a severe course compared with the normal population. Prospective studies that allow a closer follow-up of patients could provide a better understanding of the clinical course of COVID-19 in Gaucher disease.

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Table 1. Comparison of clinical and demographic parameters of COVID-19 patients with Gaucher disease and others (crude analysis, before PSM)

	Gaucher n=39	Others n=149,579	Available data (n / n)	p1
Age, years, median (IQR)	55 (25)	49 (25)	39 / 149,579	**<0.001**
Gender, male, n (%)	18 (46.2)	78,342 (52.4)	39 / 149,579	0.437
Smoking (current smoker - n,%)	3 (13.0)	22,646 (21.0)	23 / 107,621	0.347
Education (9 years and over - n,%)	3 (42.9)	8010 (36.9)	7 / 21,735	0.742
Comorbid conditions				
Hypertension, n (%)	35 (89.7)	52,143 (34.9)	39 / 149,579	**<0.001**
T2DM, n (%)	22 (57.9)	33,456 (22.5)	39 / 149,579	**<0.001**
Dyslipidemia, n (%)	28 (71.8)	23,720 (15.9)	39 / 149,579	**<0.001**
Obesity, n (%)	---	4337 (29.6)	--- / 149,579	NA
Asthma/COPD, n (%)	13 (33.3)	29,712 (19.9)	39 / 149,579	**0.035**
Chronic kidney disease, n (%)	7 (31.8)	3961 (12.0)	22 / 32,906	**0.004**
Coronary artery disease, n (%)	24 (61.5)	20,678 (13.8)	39 / 149,579	**<0.001**
Heart failure, n (%)	5 (12.8)	4973 (3.3)	39 / 149,579	**0.001**
Cancer, n (%)	6 (15.4)	5446 (3.6)	39 / 149,579	**<0.001**
Laboratory values				
CT findings of COVID-19	13 (35.1)	33,533 (24.3)	37 / 138,181	0.123
Glucose, mg/dL, median (IQR)	107 (32)	107 (37)	13 / 11,810	0.619
LDL-cholesterol, mg/dL, median (IQR)	109 (48)	114 (53)	8 / 5108	0.677
e-GFR, mL/min/1.73 m^2, median (IQR)	68 (70)	89 (37)	15 / 23,798	**0.004**
AST, >ULN, n (%)	1 (7.1)	2789 (18.4)	14 / 15,135	0.276
ALT, >ULN, n (%)	2 (13.3)	3022 (19.9)	15 / 15,190	0.525
CRP, >ULN, n (%)	12 (75.0)	17,356 (61.4)	16 / 28,261	0.264
Lactate dehydrogenase, >ULN, n (%)	7 (53.8)	5458 (37.5)	13 / 14,550	0.224
Ferritin, >100 ng/mL, n (%)	9 (69.2)	6962 (54.3)	13 / 12,815	0.281
Lymphopenia, Lym# <1000, n (%)	5 (26.3)	12671 (16.9)	19 / 74,991	0.273
Albumin, g/dL, median (IQR)	4.0 (0.9)	4.0 (0.9)	11 / 5605	0.846
Treatments				
RAS blocker, n (%)	25 (64.1)	30,111 (20.1)	39 / 149,579	**<0.001**
Statin, n (%)	22 (56.4)	11,908 (8.0)	39 / 149,579	**<0.001**
Acetylsalicylic acid, n (%)	25 (64.1)	19,258 (12.9)	39 / 149,579	**<0.001**
Outcomes				
Hospitalization, n (%)	27 (69.2)	63,901 (42.7)	39 / 149,579	**0.001**
ICU admission and/or mechanical ventilation, n (%)	3 (11.1)	8364 (13.1)	27 / 63,812	0.759
Mortality, n (%)	2 (5.1)	4785 (3.2)	39 / 149,571	0.356

Abbreviations: T2DM, type 2 diabetes mellitus; COPD, chronic obstructive pulmonary disease; CT, computerized tomography; COVID-19, coronavirus disease 2019; LDL-cholesterol, low-density lipoprotein cholesterol; e-GFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; ULN, upper limit of normal; RAS, renin-angiotensin-aldosterone system; ICU, Intensive-care unit.

Table 2. Comparison of clinical and demographic parameters of COVID-19 patients with Gaucher disease and control subjects (after PSM for age and gender)

	Gaucher n=39	Control n=39	Available data (n / n)	p-value
Age, years, median (IQR)	55 (25)	55 (25)	39 / 39	1.000
Gender, male, n (%)	18 (46.2)	18 (46.2)	39 / 39	1.000
Outcomes				
Hospitalization, n (%)	27 (69.2)	22 (56.4)	39 / 39	0.241
ICU admission and/or mechanical ventilation, n (%)	3 (11.1)	3 (13.6)	27 / 22	0.789
Mortality, n (%)	2 (5.1)	1 (2.6)	39 / 39	1.000

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; ICU, Intensive-care unit.

Table 3. Comparison of clinical and demographic parameters of COVID-19 patients with Gaucher disease and control subjects (after PSM for age, gender, hypertension, T2DM, and cancer)

	Gaucher n=38	Control n=38	Available data (n / n)	p1
Age, years, median (IQR)	55 (25)	55 (25)	38 / 38	1.000
Gender, male, n (%)	18 (46.2)	18 (46.2)	38 / 38	1.000
Comorbid conditions				
Hypertension, n (%)	34 (89.5)	34 (89.5)	38 / 38	1.000
T2DM, n (%)	22 (57.9)	22 (57.9)	38 / 38	1.000
Cancer, n (%)	6 (15.8)	6 (15.8)	38 / 38	1.000
Outcomes				
Hospitalization, n (%)	26 (68.4)	25 (65.8)	38 / 38	0.807
ICU admission and/or mechanical ventilation, n (%)	3 (11.5)	4 (16.0)	26 / 25	0.643
Mortality, n (%)	2 (5.3)	3 (7.9)	38 / 38	0.644

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; T2DM, type 2 diabetes mellitus; ICU, Intensive-care unit.

Figure 1. Multivariate associates of outcomes in patients with confirmed COVID-19

Figure 2: Kaplan-Meier survival curves of patients with Gaucher disease and others.

Figure 1. Multivariate associates of outcomes in patients with confirmed COVID-19

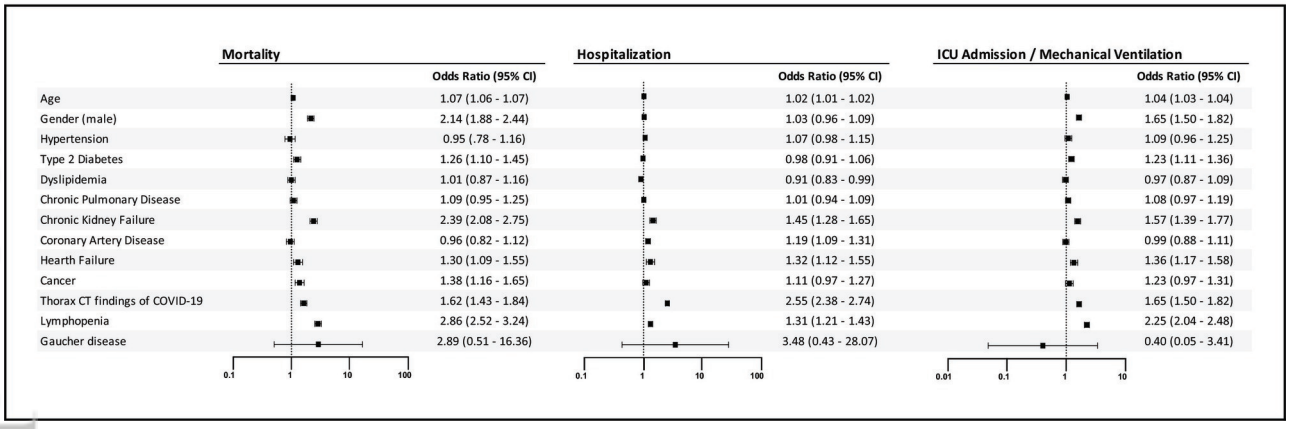

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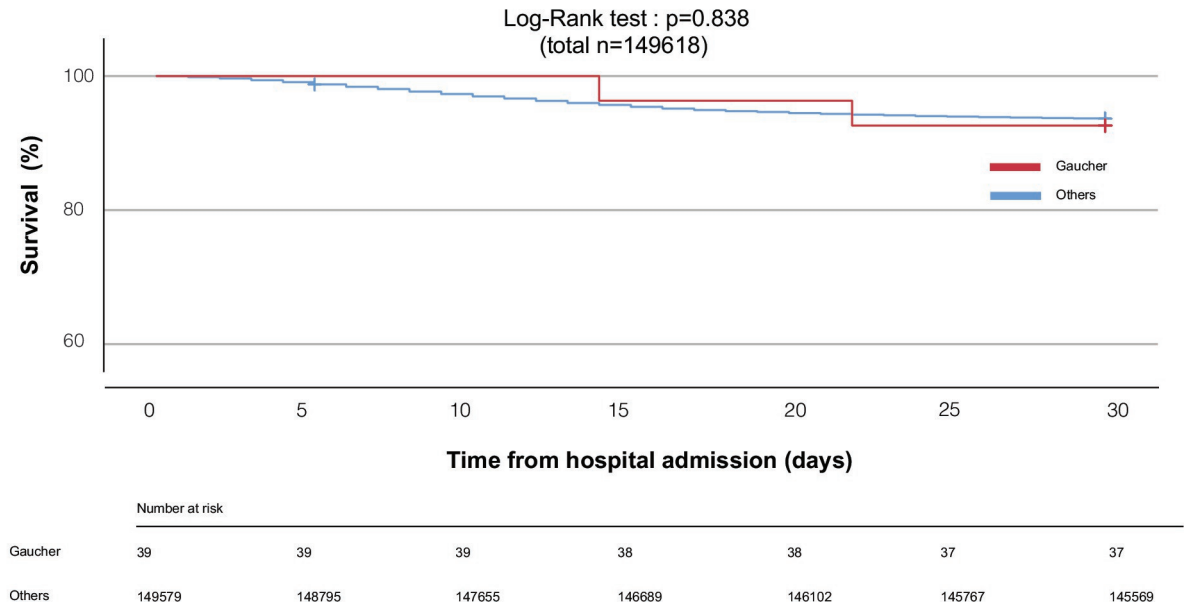
Figure 2: Kaplan-Meier survival curves of patients with Gaucher disease and others.



imj_15673_imj_15673_figure 2.eps