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Frailty is a predictor for worse outcomes in patients hospitalized with *Clostridioides difficile* infection

Abdelkader Chaar[a,b], Jin Woo Yoo[a,b], Ahmad Nawaz[c], Rabia Rizwan[a,b], Osama Qasim Agha[d], Paul Feuerstadt[e,f]

Yale School of Medicine, New Haven, CT; SUNY Upstate Medical University, Syracuse, NY; Creighton University/St. Joseph Medical Center, Phoenix, AZ; PACT-Gastroenterology Center, Hamden CT, USA

Abstract

Background Frailty has major health implications for affected patients and is widely used in the perioperative risk assessment. The Hospital Frailty Risk Score (HFRS) is a validated score that utilizes administrative billing data to identify patients at higher risk because of frailty. We investigated the utility of the HFRS in patients with *Clostridioides difficile* infection (CDI) to determine whether they were at risk for worse outcomes and higher healthcare resource utilization.

Methods Using the 2017 National Inpatient Sample, we identified all adults with a primary diagnosis of CDI. We classified patients into 2 groups: those who had an HFRS <5 (NonFrailCDI) and those with a score ≥5 (FrailCDI). We assessed differences in hospital outcomes and healthcare resource utilization based on frailty status.

Results We identified 93,810 hospitalizations, of which 54,300 (57.88%) were FrailCDI. FrailCDI patients were at higher risk for fulminant CDI (odds ratio [OR] 1.9, 95% confidence interval [CI] 1.6-2.3), requiring colectomy (OR 4.1, 95%CI 1.5-11.2), and inpatient mortality (OR 4.5, 95%CI 2.8-7.1). Furthermore, FrailCDI patients had higher odds of requiring Intensive Care Unit admission (OR 13.7, 95%CI 6.3-29.9) or transfer to another facility on discharge (OR 2.2, 95%CI 2.0-2.4), and had longer hospital stays and higher total charges when compared with NonFrailCDI.

Conclusions Frailty as defined by the HFRS is an independent factor for worse outcomes and higher healthcare utilization in adults admitted for CDI. Risk stratifying patients by frailty may improve outcomes.

Keywords *Clostridioides difficile,* colitis, frailty, Hospital Frailty Risk Score

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Introduction

Clostridioides difficile infection (CDI) is the most common healthcare-associated infection in the United States of America (USA) [1], and is associated with significant morbidity and mortality in hospitalized patients. Multiple risk factors are recognized as contributors to developing CDI, including recent antimicrobial use within the last 2 months, taking a proton pump inhibitor, greater healthcare exposure, and advanced age [2]. Patients older than 65 years have a 5- to 10-fold higher risk of CDI compared to those younger than 65 years, and are associated with worse outcomes [3].

With the rapid increase in the proportion of the population older than 65, factors other than age are being recognized as important predictors of outcomes; examples of such factors include comorbidities, disability, nutrition status, and loss of muscle mass. Frailty has emerged as a more comprehensive

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Correspondence to: Paul Feuerstadt, MD, FACG, AGAF, 2200 Whitney Avenue, Hamden, CT 06518, USA,
e-mail: pfeuerstadt@gastrocenter.org

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predictor for worse clinical outcomes. Frailty is defined as a state of increased susceptibility to poor homoeostasis resolution following a stressor event, which raises the risk of unfavorable consequences, such as falls, delirium and disability [4]. Frailty has been used as a predictor for worse outcomes in the perioperative period, oncology patients, and multiple other medical conditions [5-8]. The literature evaluating the association between frailty and outcomes in patients with CDI is very limited, and most studies have focused on functional status and advanced age, rather than frailty itself as a constellation of comorbidities [9,10].

The Hospital Frailty Risk Score (HFRS) is a validated score that predicts the risk associated with frailty [11-16]. The HFRS is easy to implement using administrative billing data, and has demonstrated predictive value for worse outcomes and mortality among hospitalized patients [7,8,17]. In this study, we evaluated a cohort of inpatients with CDI from a national database within the USA, considering the prevalence of frailty status among this population, and subsequently evaluating its association with clinical outcomes and healthcare utilization for adult patients.

Patients and methods

Study design and data source

This was a population-based retrospective cohort study using the National Inpatient Sample (NIS) from 2017. This database has been developed for the Healthcare Cost and Utilization Project by the Agency for Healthcare Research and Quality. It is the largest publicly available all-payer database for inpatient care in the USA, containing data on more than 7 million unweighted inpatient admissions. The NIS includes approximately a 20% stratified sample of all discharges from USA community hospitals, excluding rehabilitation and long-term acute care hospitals. In 2017, the NIS was sampled from 4584 hospitals in 48 states [18]. The database contains both patient and hospital-level variables. Each patient has up to 40 discharge diagnoses and up to 25 procedures, using the International Classification of Diseases, 10th revision, clinical modification (ICD-10-CM) coding system.

Patient population and study variables

We included adult patients (≥18 years old) who had a primary discharge diagnosis of CDI, dividing them into those who were frail (FrailCDI) and those who were not (NonFrailCDI). Variables considered included age, sex, race/ethnicity (Caucasian, African American, Hispanic, Asian or Pacific Islander, Native American, and other), median household income quartile (Quartile 1: $1-$43,999; Quartile 2: $44,000-$55,999; Quartile 3: $56,000-$73,999; and quartile 4: $74,000+), primary insurance provider (Medicare, Medicaid, private insurance and uninsured), hospital size (small, medium, large), and location/teaching status of the hospital (rural, urban nonteaching, urban teaching). We calculated rates for various medical comorbidities in addition to the Charlson comorbidity index.

[a]Department of Internal Medicine, Yale School of Medicine, New Haven, CT (Abdelkader Chaar, Jin Woo Yoo, Rabia Rizwan); [b]Department of Medicine, Yale-New Haven Hospital, New Haven, CT (Abdelkader Chaar, Jin Woo Yoo, Rabia Rizwan); [c]Division of Gastroenterology, SUNY Upstate Medical University, Syracuse, NY (Ahmad Nawaz); [d]Creighton University/St Joseph Medical Center, Phoenix, AZ (Osama Qasim Agha); [e]Section of Digestive Diseases, Yale School of Medicine, New Haven, CT (Paul Feuerstadt); [f]PACT-Gastroenterology Center, Hamden, CT (Paul Feuerstadt), USA

Definition of frailty - HFRS

We defined frailty using the HFRS, a score based on ICD-10 codes that was developed by Gilbert *et al* in 2018 [16], and was subsequently validated in multiple studies [11-15]. The score is calculated from 109 ICD-10 codes representing the conditions that were found to be most associated with frailty. Each code is assigned a certain score/weight from 0.1 to 7.1, depending on the likelihood of being associated with frailty. To calculate the HFRS, we add the scores corresponding to the set of ICD-10 codes for each patient. The following HFRS cutoffs are used to categorize patients' risk for frailty: <5 low frailty risk; 5-15 intermediate frailty risk; and >15 high frailty risk. For simplicity, we divided our cohort into 2 groups: patients with HFRS <5 were considered at low risk for frailty (NonFrail), while those with HFRS ≥5 were considered moderate to high risk for frailty (Frail).

Outcomes

Outcomes included in-hospital mortality, morbidity (ileus, intestinal perforation, admission to Intensive Care Unit [ICU], acute kidney injury requiring dialysis, artificial nutrition, and fulminant CDI), and need for surgical intervention, including in-hospital colectomy or diverting loop ileostomy. In addition, we evaluated various healthcare utilization metrics, including length of stay, total hospital charges, and disposition destination at the time of discharge (home vs. transfer to a facility).

"Fulminant CDI" was defined as a composite outcome of having a diagnosis of ileus, requiring surgical intervention, or inpatient mortality. "Requiring dialysis" was defined as the presence of ICD-10 procedure codes for dialysis, which was performed on day 3 of the admission or later; this approach helps by excluding patients who were on chronic dialysis at the time of admission. We compared outcomes between those who met the frailty definition and those who did not. To assess whether frailty increases the risk for worse outcomes in younger patients, we performed subgroup analyses for the outcome of severe CDI and non-routine disposition among FrailCDI and NonFrailCDI, based on age groups in 10-year intervals.

Statistical analysis

Categorical variables are presented as percentages, while continuous variables are presented as means with standard

deviations, unless otherwise specified. We compared categorical variables using the chi-square and continuous variables using Student's *t*-test. We conducted a multivariate regression analysis to assess the effect of frailty status on different outcomes, after adjusting for age, sex, race, hospital location and teaching status, insurance, median household income, and Charlson comorbidity index. All statistical analyses were performed using Stata, version 17.0 (StataCorp, College Station, Texas, USA). The Stata survey commands were used to account for clustering, stratification, and weighting of data in the NIS to provide national estimates. A P-value <0.05 was considered statistically significant.

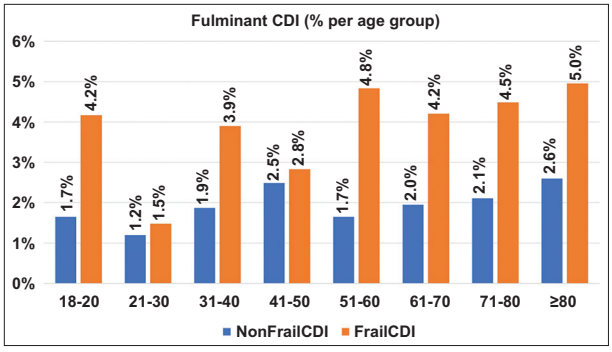

Figure 1 Rates of fulminant *Clostridioides difficile* infection (CDI) among FrailCDI and NonFrailCDI patients, divided into different age groups

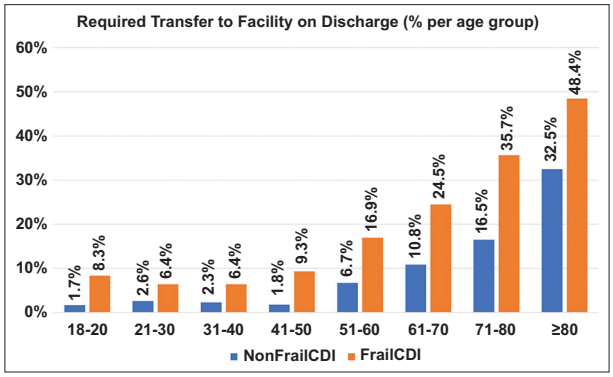

Figure 2 Rates of patients who required transfer to a facility among FrailCDI and NonFrailCDI patients divided into different age groups
CDI, Clostridioides difficile infection

Results

Patients and hospital characteristics

A total of 93,810 hospitalizations were identified; the patients' mean age was 66.1 years and 64.2% were female. Of these, 54,300 (57.9%) were FrailCDI while 39,510 (42.1%) were NonFrailCDI. When compared to NonFrailCDI, FrailCDI patients were older (mean age 60.1 vs. 70.5 years; P<0.001), had lower income (28.6% vs. 26.6% within 0-25th percentile of household income; P=0.035), and most of them were on Medicare (75.5% vs. 52.2%; P<0.001). We also noted racial differences between FrailCDI and NonFrailCDI (Whites: 78.5% vs. 76.8%, Blacks: 11.1% vs. 10.1%, and Hispanics: 6.7% vs. 8.9%; P<0.001). There were no differences between the groups in the distribution of hospital size, location or teaching status (Table 1).

Clinical outcomes and healthcare utilization

FrailCDI patients required mechanical ventilation (1.1% vs. 0.1%; P<0.001), enteral nutrition (0.5% vs. 0.2%; P<0.001), and developed ileus (2.3% vs. 1.6%; P<0.001) more frequently than NonFrailCDI. Additionally, more FrailCDI patients required colectomy (0.3% vs. 0.1%; P<0.001) or diverting loop ileostomy (0.3% vs. 0.1%; P<0.001).

In terms of healthcare resource utilization, FrailCDI patients had longer hospital stays (mean 6.3 vs. 4.2 days; P<0.001) and greater total hospital charges (mean $44,180 vs. $30,908; P<0.001). On discharge, more FrailCDI patients required transfer to a facility (31.9% vs. 11.9%; P<0.001) (Table 2).

Subgroup analysis of different age groups

In all age groups, FrailCDI patients had higher rates of severe CDI and were more likely to require transfer to a facility upon discharge, as compared with NonFrailCDI (Fig. 1, 2).

Results of multivariate analysis

After adjusting for demographics and Charlson comorbidity index, multivariate analysis showed that FrailCDI patients were at higher risk for fulminant CDI (odds ratio [OR] 1.9, 95% confidence interval [CI] 1.6-2.3; P<0.001), more frequent need for colectomy (OR 4.1, 95%CI 1.5-11.2; P<0.001), and higher inpatient mortality (OR 4.5, 95%CI 2.8-7.1; P<0.001). In addition, FrailCDI patients were more likely to require an ICU level of care (OR 13.7, 95%CI 6.3-29.9; P<0.001) or transfer to another facility at the time of discharge (OR 2.2, 95%CI 2.0-2.4; P<0.001), while they also had longer hospital stays (adjusted coefficient 1.7, 95%CI 1.6-1.9; P<0.001) along with higher total charges (adjusted coefficient 11,843.6, 95%CI 10,366.3-13,320.8; P<0.001) compared with NonFrailCDI patients (Table 3).

Discussion

The HFRS is a validated clinical tool for assessing patients' frailty, based on readily available billing codes, and hence prognosticating their risk of adverse clinical outcomes. In our analysis of a large nationally representative USA sample, 58% of all CDI discharges were found to have an HFRS score ≥5, indicating that a large portion of adult CDI patients had significant frailty. FrailCDI patients were at significantly higher risk for worse clinical outcomes and greater healthcare utilization, compared with NonFrailCDI. A younger cohort

Table 1 Baseline characteristics of frail and non-frail patients with Clostridioides difficile infection (CDI)

Characteristics	NonFrailCDI n=39,510	FrailCDI* n=54,300	P-value
Female sex, %	63.9	64.3	0.611
Age (years), mean ± standard deviation	60.1±18.6	70.5±15.4	<0.001
Age ≥65 years, %	44.5	69.5	<0.001
Age category, %			
31-40	9.5	3.1	
41-50	12.7	6.2	
51-60	17.6	11.9	
61-70	19.5	19.9	
71-80	16.8	25.4	
81-90	16.1	31.4	
Race/ethnicity, %			<0.001
White	76.8	78.5	
Black	10.1	11.1	
Hispanic	8.9	6.7	
Asian or Pacific Islander	1.2	1.4	
Native American	0.6	0.6	
Other	2.3	1.6	
Median household income, %			0.035
0-25th percentile	26.6	28.6	
26-50th percentile	27.9	27.4	
51-75th percentile	24.5	23.3	
76-100th percentile	20.9	20.7	
Primary payer, %			<0.001
Medicare	52.2	75.5	
Medicaid	14.0	8.3	
Private insurance	27.7	13.4	
Self-pay	3.5	1.5	
No charge	0.5	0.1	
Other	2.1	1.2	
Region of hospital, %			<0.001
Northeast	20.4	17.5	
Midwest	23.4	25.7	
South	40.2	39.2	
West	16.1	17.5	
Hospital size, %			0.283
Small	21.9	20.9	
Medium	30.0	30.4	
Large	47.9	48.7	
Hospital location, %			0.629
Rural	11.2	11.4	
Urban	88.8	88.6	
Teaching status, %			0.756
Rural	11.2	11.40	
Urban non-teaching	26.1	26.4	
Urban teaching	62.7	62.2	
Charlson comorbidity index	1.6±1.9	2.8±2.3	<0.001
Hospital Frailty Risk Score, mean ± SD	2.6±1.5	8.9±3.3	<0.001
Comorbidities, %			
Alcohol use	4.3	5.2	0.004
Chronic kidney disease on dialysis	3.6	6.3	<0.001
Coronary artery disease	16.3	26.4	<0.001
Diabetes	23.0	33.2	<0.001
Heart failure	10.5	21.4	<0.001
Hypertension	53.8	62.6	<0.001
Inflammatory bowel disease	9.9	4.5	<0.001
Metastatic cancer	3.4	3.9	0.055
Morbid obesity	5.5	5.9	0.195
Non-alcoholic hepatic steatosis	0.4	0.6	0.090
Obesity	11.4	11.8	0.354
Smoking	33.9	38.7	<0.001

*Frail=Hospital Frailty Risk Score ≥5

SD, standard deviation

Table 2 Outcomes of frail and non-frail group with *Clostridioides difficile* infection (CDI)

Outcomes	NonFrailCDI n=39,510	FrailCDI n=54,300	P-value
ICU requirement:			
Vasopressor use, %	0.03	0.29	0.002
Mechanical ventilation, %	0.08	1.13	<0.001
ICU, %	0.1	1.3	<0.001
Ileus, %	1.6	2.3	<0.001
Perforation, %	0.1	0.2	0.404
Total parenteral nutrition, %	0.6	0.8	0.149
Enteral nutrition, %	0.2	0.5	<0.001
Dialysis initiation, %	0.1	0.2	0.065
Required surgical intervention, %			
Colectomy	0.1	0.3	<0.001
Diverting loop ileostomy	0.1	0.3	0.001
In-hospital all-cause mortality, %	0.3	2.1	<0.001
Fulminant CDI[a], %	2.0	4.5	<0.001
Disposition, %			<0.001
Home[b]	88.1	68.1	
Transfer to facility[c]	11.9	31.9	
Length of stay (days), mean ± SD	4.2±3.4	6.28±6.5	<0.001
Total charges ($), mean ± SD	30,908.3±34,174.5	44,180.5±57,287.3	<0.001

[a]Composite outcome defined as having a diagnosis of ileus, requiring surgical intervention, or inpatient mortality

[b]Home discharge, including self-care, home health care, and against medical advice

[c]Transfer to facility, including transfer to short-term hospital, skilled nursing facility, intermediate care, or another transfer type of facility

CDI, Clostridioides difficile infection; ICU, intensive care unit; SD, standard deviation

Table 3 Multivariate regression for the outcomes of FrailCDI patients compared to NonFrailCDI patients. Analysis adjusted for age, sex, race, hospital location and teaching status, insurance, median household income and Charlson comorbidity index

Outcome	Adjusted odds ratio	95% confidence interval	P-value
Total charges ($)	11,843.6*	[0,366.3-13,320.8	<0.001
TPN requirement	1.6	1.1-2.4	0.022
Enteral nutrition	3.3	1.7-6.5	<0.001
ICU requirement	13.7	6.3-29.9	<0.001
Vasopressor use	12.6	2.9-53.7	0.001
Mechanical ventilation	16.1	6.4-40.3	<0.001
Colectomy	4.1	1.5-11.2	0.007
Diverting loop ileostomy	3.2	1.3-7.9	0.014
Fulminant CDI	1.9	1.6-2.3	<0.001
In-hospital mortality	4.5	2.8-7.1	<0.001
Length of Stay (days)	1.7*	1.6-1.9	<0.001
Transfer to facility	2.2	2.0-2.4	<0.001

*Adjusted coefficient

CDI, Clostridioides difficile infection; ICU, intensive care unit; TPN, total parenteral nutrition

with higher HFRS showed similar differences, suggesting that the HFRS may be a useful tool for predicting poor outcomes in a broad population with CDI.

There are currently limited data regarding the association of frailty with CDI outcomes. A recent Danish study of 457 elderly patients (≥60 years) with first-time CDI found that those with severe levels of frailty (measured by a multidimensional prognostic index based on clinical assessment tools) were 10 times more likely to die within 90 days than those with low frailty levels, after adjustment for age and sex (hazard ratio [HR] 10.2, 95%CI

4.1-25.4; P<0.001). Frailty was a better predictor of mortality than both age (P<0.001) and CDI severity (defined as albumin <30 g/L, leucocytes >15×10^9/L, or abdominal pain) (P=0.04) with a receiver operating characteristic curve area of 77% [19].

The HFRS is a validated predictor for poor outcomes in various other medical conditions. In those with inflammatory bowel disease, frailty prevalence was low overall (6%), but was independently associated with a greater risk of mortality (OR 2.9, 95%CI 2.3-3.7) [20]. In a retrospective study that included 16,561 USA veterans with cirrhosis, frailty was associated with a greater likelihood of acute on chronic liver failure hospitalizations (OR 1.03 per HFRS point, 95%CI 1.02-1.03) and worse long-term survival from the time of hospitalization (HR 1.02 per 5 HFRS points, 95%CI 1.01-1.04) [7]. Furthermore, frail cardiac arrest survivors and patients admitted with exacerbations of chronic obstructive pulmonary disease were less likely to be discharged home [8].

Malnutrition is known to be associated with frailty [21]. Our study further supports this concept. In our study, FrailCDI patients were more likely to require total parenteral nutrition (OR 1.6, 95%CI 1.1-2.4) and enteral nutrition (OR 3.3, 95%CI 1.7-6.5), suggesting the importance of nutritional status in frail patients. Nutritional status is frequently overlooked, but its importance is probably greater than most clinicians consider.

We believe that determining frailty in CDI patients on admission can contextualize risk for these patients by rapidly identifying those at high risk, and potentially informing clinical decisions in real time. Given their greater risk of severe disease and associated complications, frail CDI patients warrant close monitoring of their response to therapy, disease progression, and development of complications; this should include serial physical exams, laboratory tests and imaging modalities. Notably, in our study, frail CDI patients were found to have 4-fold higher odds of requiring in-hospital colectomy. This is an important observation, and reflects the severity of CDI in this population. However, it is important to recognize that frailty itself may also be associated with perioperative adverse events. One study showed frailty to be associated with greater morbidity and mortality following colectomy for CDI patients, underscoring the importance of including a consideration of frailty in shared decision-making [22]. These measures may improve not only patient outcomes, but also efficiency of care, by potentially reducing ICU requirements, consultation needs, transfers to healthcare facilities on discharge, lengths of hospital stay, and overall healthcare resource utilization and its associated costs.

Our study gains its strength from the well-defined, large nationally representative sample. It is, to the best of our knowledge, the first to provide such a large-scale evaluation of the relationship between CDI outcomes and frailty. The HFRS can be computed quickly using readily available administrative hospital data, enabling effective implementation in practice to inform clinical decisions in real time, regardless of the patient volume or the level of acuity. Concomitantly, it also facilitates further research into the disease-specific impact of frailty on clinical outcomes.

There are limitations to our study, most of which are inherent to its observational retrospective nature. Computed purely from established ICD-10 codes, our analysis did not evaluate clinical details, such as physical exam findings, laboratory values, radiographic data and specific treatments, that may be pertinent to the severity of underlying comorbidities. The data also did not include details about important CDI risk factors, such as recent healthcare exposure, antibiotics or proton-pump inhibitor use. We were able to account for the comorbid burden by including the Charlson comorbidity index in our multivariate regression analysis, although unmeasured confounding that may have influenced our observed associations is still possible, given the nature of this database. It is possible that our analysis underestimated the total number of CDI cases in hospitalizations where CDI was coded as a secondary diagnosis; we intended to specifically choose those with a principal CDI diagnosis to ensure we only studied hospitalizations primarily attributable to CDI. The use of ICD-10 codes is also subject to potential misclassification of diagnoses, but such errors might be expected to be distributed equally across both FrailCDI and NonFrailCDI groups.

In conclusion, frailty status as defined by the HFRS is an independent factor associated with worse clinical outcomes and higher healthcare resource utilization in adult patients admitted for CDI. These results shed light on the utility of the HFRS as a clinical prognostic tool to risk-stratify patients with CDI on admission, inform clinical decisions in real time by identifying those who warrant aggressive treatment and monitoring, and ultimately improve patient outcomes. Incorporating the HFRS into electronic medical records as a readily available, easy-to-use, rapid clinical calculator may help improve clinical outcomes in this vulnerable population.

Summary Box

What is already known:

- *Clostridioides difficile* infection (CDI) is a healthcare-associated infection that affects hospitalized patients and can result in significant morbidity and mortality
- Frailty is a predictor of worse clinical outcomes that has been used in the perioperative period for oncology patients and multiple other medical conditions
- The Hospital Frailty Risk Score (HFRS) is an easy-to-implement, validated score that predicts the risk of frailty, and has demonstrated predictive value for worse outcomes and mortality among hospitalized patients
- Limited data are available about the association between frailty and outcomes in those with CDI

What the new findings are:

- Frailty as defined by HFRS is an independent factor for worse outcomes and higher healthcare resource utilization in adults admitted for CDI
- The HFRS may be used as a clinical prognostic tool to risk-stratify patients hospitalized with CDI

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