Original Research

A Retrospective Study of Admission NT-proBNP Levels as a Predictor of Readmission Rate, Length of Stay and Mortality

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Abstract

Introduction
Serum levels of pro-B-type natriuretic peptide (BNP) and N-terminal (NT) proBNP are measured at admission to assess the likelihood of acutely decompensated heart failure (ADHF). Elevated NT-proBNP levels on initial presentation are a reliable marker of ADHF. However, the prognostic significance of NT-proBNP levels measured on admission remains unknown. With a better understanding of how admitting NT-proBNP levels impacts readmission rates, length of stay and mortality, future prospective studies with specific interventions can be developed to reduce all-cause readmissions, shorten length of stay and reduce mortality.

Methods
In this retrospective study, we evaluated heart failure with reduced ejection fraction (HFrEF) admissions from 2017–2018 with a focus on 30-, 60- and 90-day all-cause readmissions, length of stay (LOS) and in-hospital mortality rate that are predicted by NT-proBNP levels measured on admission. Using the HCA Healthcare Enterprise Data Warehouse, adult patients age 18 to 75 were selected using admission ICD-10 codes for HFrEF. Dialysis patients were excluded. Our search of 90 hospitals yielded 21,445 patients who were stratified into quartiles depending on their admission NT-proBNP levels: group 1 (<1669 pg/ml), group 2 (1670–4274 pg/ml), group 3 (4275–10,499 pg/ml) and group 4 (>10,500 pg/ml).

Results
Readmission Rates: The 60-day all-cause readmission was significantly ($p = 0.047$) higher in group 4 compared to group 1 (adjusted odds ratio (OR) = 1.116, $p = 0.013$) and group 2 (adjusted OR = 1.111, $p = 0.014$). The 90-day all cause readmission for group 4 was also significantly higher when compared to group 1 (adjusted OR = 1.105, $p = 0.021$).

Length of Stay: Elevated NT-proBNP concentrations were associated with a significantly longer LOS ($p < 0.0005$). Pairwise, comparisons and estimates for adjusted LOS showed a positive linear association between higher NT-proBNP groups and longer LOS.

Mortality: Higher inpatient mortality rates were associated with elevated NT-proBNP levels. The mortality rate was 0.9% in group 1 compared to a 4.7% mortality rate in group 4. Adjusted OR for mortality increased with increasing levels of NT-proBNP.

Conclusions
Based on the analysis, higher admitting NT-proBNP levels were associated with significantly higher 60-day all-cause readmission, longer LOS and increased mortality. These findings suggest that measuring NT-proBNP levels at admission may provide an indication of patient outcomes. Prospective studies with targeted strategies can be developed to reduce readmissions, shorten LOS and reduce mortality based on admission NT-proBNP levels.

Keywords
NT-proBNP; BNP; brain natriuretic peptide; peptide fragments; nerve tissue proteins; heart failure; patient readmission; readmission rates; hospital mortality; length of stay

Introduction

Serum levels of pro-B-type natriuretic peptide (BNP) and N-terminal (NT) pro-BNP are routinely measured at the time of admission for patients with shortness of breath to assess the risk of acutely decompensated heart failure (ADHF). Pro-BNP, released by the myocardium due to cardiac wall distention, is cleaved into the active BNP and inactive NT-proBNP forms.[1] Elevated levels of NT-proBNP are a reliable marker of ADHF,[2] but the time of measurement varies, which could be affected by treatment. Fisher et al. found that NT-proBNP levels, measured just prior to discharge, were predictive of mortality and readmission.[3] Flint et al. examined NT-proBNP levels at the time of discharge and observed that patients with levels >1000 ng/L had a 15% higher 30-day readmission rate.[4] The levels of NT-proBNP are expected to be more stable at discharge after patients have been treated for ADHF and, therefore, may not accurately reflect the ventricular function.[1] Measuring NT-proBNP at admission, when the patient is acutely ill and seeking treatment, may be more predictive of patient outcomes. However, the prognostic significance of the levels of NT-proBNP at the time of initial admission remains unknown.[1,3]

With a better understanding of how admitting NT-proBNP levels impacts all-cause readmission rates, length of stay (LOS) and mortality, further prospective studies are warranted to develop specific interventions during systolic heart failure admissions to reduce length of stay, mortality and reduce readmissions. The purpose of this study was to determine whether NT-proBNP, measured on patient admission, provided an indication of outcome when a patient was admitted for HFrEF. We hypothesized that patients with higher levels of NT-proBNP would have higher readmission rates, longer length of stay and higher rates of mortality.

Methods

Study Design

In this retrospective study, we evaluated heart failure with reduced ejection fraction (HFrEF) admissions from 2017–2018. We also analyzed 30-, 60- and 90-day all-cause readmission rates, LOS and mortality rate and compared them to the NT-proBNP levels at the time of admission. Using the HCA Healthcare Enterprise Data Warehouse (EDW), we identified patients aged 18 to 75 years old using admitting ICD-10 codes for acute systolic heart failure. Dialysis and patients under the age of 18 were excluded, and our extraction yielded 21,445 patients. These patients were grouped into quartiles based on the admission NT-proBNP levels: group 1 (<1,669 pg/ml), group 2 (1,670–4,274 pg/ml), group 3 (4,275–10,499 pg/ml) and group 4 (>10,500 pg/ml).

Patient Population

Our patient population includes those 18 to 75 years of age who were admitted from January 2017 to December 2018 with an admitting ICD-10 code for HFrEF. Dialysis patients were excluded.

Outcomes

The primary outcomes of interest were all-cause readmission rate, length of stay and mortality.

Statistical Analysis

In order to summarize patient characteristics and comorbidities, descriptive statistics were used. Multivariate comparisons of patient characteristics, comorbidities and outcomes (all-cause readmission, LOS and mortality) were conducted. Statistical significance was evaluated using $\alpha = 0.05$. Multiple logistic regression was performed to identify differences in readmissions and mortality. Adjusted odds ratios and p-values between BNP groups were calculated from these multiple logistic regression analyses. LOS analysis was done with an ANCOVA model with post hoc pairwise comparisons.

Results

Demographics Data

Table 1 summarizes the demographics for patients (n = 21,445) included in the data set. Sample patients were more likely to be Caucasian males (63.2%) with the average age ranging from 60–62.9 years among the quartiles. The highest comorbidities within the study group were coronary artery disease (CAD), diabetes mellitus (DM), COPD, chronic kidney disease (CKD) and obesity (BMI >30). Regarding CKD, higher levels of NT-proBNP were associated with a glomerular filtration rate (GFR) of <44 mm/min.

Table 1. Demographics.

	Group 1 NT-proBNP <1,669 (n = 5,360)	Group 2 NT-proBNP 1,670–4,274 (n = 5,362)	Group 3 NT-proBNP 4,275–10,499 (n = 5,362)	Group 4 NT-proBNP >10,500 (n = 5,361)	p Value
Age					<0.0005
Average age (years) (mean +SD)	60.0 +10.75	60.8 +10.95	61.7 +10.76	62.9 +10.35	
Sex					<0.0005
Male	3,742 (69.8%)	3,801(70.8%)	3,684 (68.7%)	3,355 (62.5%)	
Race					0.026
Caucasian	3,728 (69.6%)	3,614 (67.4%)	3,605 (67.2%)	3,654 (68.1%)	
African American	1,199 (22.4%)	1,332 (24.8%)	1,279 (23.9%)	1,261 (23.5%)	
Other	433 (8.1%)	416 (7.8%)	478 (8.9%)	446 (8.3%)	
Medical History					
HTN	920 (17.2%)	809 (15.1%)	746 (13.9%)	505 (9.4%)	<0.0005
ACS	77 (1.4%)	65 (1.2%)	56 (1.0%)	56 (1.0%)	0.192
PCI during hospital stay	73 (1.4%)	73 (1.4%)	77 (1.4%)	97 (1.8%)	0.170
CAD	2,729 (50.9%)	2,732 (51.0%)	2,871 (53.5%)	3,039 (56.7%)	<0.0005
Atrial fibrillation	933 (17.4%)	1,204 (22.5%)	1,165 (21.7%)	1,010 (18.8%)	<0.0005
Prior ICD	754 (14.1%)	784 (14.6%)	773 (14.4%)	760 (14.2%)	0.848
Prior pacemaker	352 (6.6%)	351 (6.5%)	373 (7.0%)	349 (6.5%)	0.769
COPD	1,839 (34.3%)	1,746 (32.6%)	1,802 (33.6%)	1,903 (35.5%)	0.012
Asthma	411 (7.7%)	320 (6.0%)	352 (6.6%)	283 (5.3%)	<0.0005
CKD	1,189 (22.2%)	1,821 (34.0%)	2,356 (43.9%)	3,631 (67.7%)	<0.0005
Admission GFR: ≥45	4,632 (86.4%)	4,238 (79.0%)	3,779 (70.5%)	2,190 (40.9%)	<0.0005
Admission GFR: 30-44	508 (9.5%)	757 (14.1%)	990 (18.5%)	1,194 (22.3%)	
Admission GFR: 15-29	191 (3.6%)	322 (6.0%)	469 (8.7%)	1,097 (20.5%)	
Admission GFR: <15	29 (0.5%)	45 (0.8%)	124 (2.3%)	880 (16.4%)	
Diabetes mellitus	2,607 (48.6%)	2,677 (49.9%)	2,556 (47.7%)	2,789 (52.0%)	<0.0005
Obesity (BMI>30)	1,025 (19.1%)	884 (16.5%)	751 (14.0%)	529 (9.9%)	<0.0005
Alcohol abuse	199 (3.7%)	260 (4.8%)	210 (3.9%)	175 (3.3%)	<0.0005
Tobacco abuse	99 (1.8%)	102 (1.9%)	102 (1.9%)	105 (2.0%)	0.981

Abbreviations: HTN: hypertension, ACS: acute coronary syndrome, PCI: percutaneous coronary intervention, CAD: coronary artery disease, ICD: implantable cardioverter-defibrillator, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, GFR: glomerular filtration rate, BMI: body mass index

All-cause Readmission Rates

The 30-day all-cause readmission rates were 26.7, 26.9, 27.7 and 30.6% respectively for the quartiles (groups 1–4). The 60-day readmission rates were 37.4, 37.8, 39.3 and 42.8% respectively for the quartiles. The 90-day readmission rates were 42.9, 43.8, 48.2 and 48.2% respectively. The 60-day readmission rates, however, were the only statistically significant readmission period (p = 0.047).

Figure 1. All-cause readmission rate by NT-proBNP group.

Intra-group analysis showed that group 4 (NT-proBNP >10,500) had a significantly higher rate of 60-day all cause readmission compared to group 1 (adjusted odds ratio (OR) = 1.116, p = 0.013) and group 2 (adjusted OR = 1.111, p = 0.014). Group 4 was also significantly higher than group 1 (adjusted OR = 1.105, p = 0.021) for 90-day readmission (**Figure 1** and **Table 2**).

Table 2. All-cause Readmission Rates by NT-proBNP.

30 Day Readmission Rate: p = 0.202			
Adjusted Odds Ratio			
BNP(a)\BNP(b)	1,670–4,274	4,275–10,499	>10,500
<1,669	0.997 (p = 0.947)	1.029 (p = 0.522)	1.092 (p = 0.066)
1,670–4,274	-	1.032 (p = 0.474)	1.095 (p = 0.051)
4,275–10,499	-	-	1.062 (p = 0.185)
60 Day Readmission Rate: p = 0.047			
Adjusted Odds Ratio			
BNP(a)\BNP(b)	1,670–4,274	4,275–10,499	>10,500
<1,669	1.005 (p = 0.904)	1.052 (p = 0.212)	1.116 (p = 0.013)
1,670–4,274	-	1.047 (p = 0.252)	1.111 (p = 0.014)
4,275–10,499	-	-	1.061 (p = 0.154)
90 Day Readmission Rate: p = 0.115			
Adjusted Odds Ratio			
BNP(a)\BNP(b)	1,670–4,274	4,275–10,499	>10,500
<1,669	1.029 (p = 0.474)	1.064 (p = 0.118)	1.105 (p = 0.021)
1,670–4,274	-	1.035 (p = 0.385)	1.075 (p = 0.088)
4,275–10,499	-	-	1.039 (p = 0.355)

The 60-day readmission rates were the only statistically significant readmission period (p = 0.047). Intra-group analysis showed that group 4 had a significantly higher rate of 60-day all cause readmission compared to group 1 (adjusted OR = 1.116, p = 0.013) and group 2 (adjusted OR = 1.111, p = 0.014). Group 4 also was also significantly higher than group 1 (adjusted OR = 1.105, p = 0.021) for 90-day readmission.

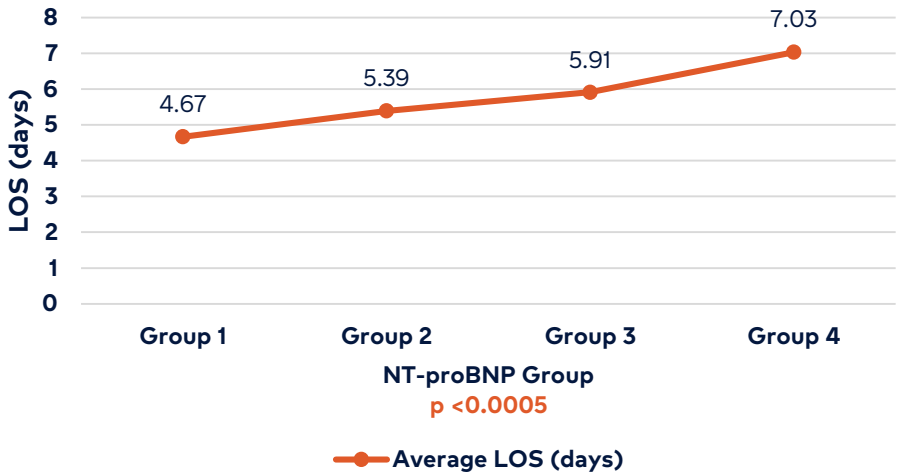

Figure 2. Average length of stay by NT-proBNP group. (LOS: length of stay)

Length of Stay

Length of stay showed a positive linear association of a higher length of stay with increasing NT-proBNP levels. The median length of stay was 4.67, 5.39, 5.91 and 7.03 days respectively for groups 1, 2, 3 and 4. Pairwise, comparisons for adjusted LOS showed a positive correlation between the higher NT-proBNP groups and a longer LOS with a p <0.0005. (**Figure 2**)

Mortality

In-hospital mortality rate increased with higher quartiles of admission NT-proBNP levels. In-hospital mortality rates were 0.9, 1.4, 2.5 and 4.7% for groups 1, 2, 3 and 4 respectively (p <0.0005). (**Figure 3**) Computing adjusted OR for mortality within each group revealed progressively higher OR across the groups. Most notably, group 4 had a 4.789 adjusted OR for mortality compared to group 1 (p <0.0005), 3.013 odds compared to group 2 (p <0.0005) and 1.802 adjusted OR for death compared to group 3 (p <0.0005). (**Table 3**)

Discussion

Our primary aim in this study was to identify NT-proBNP levels that would predict readmission rates, length of stay (LOS) and mortality. We found that patients in the highest quartiles of NT-proBNP on admission had statistically higher 60-day all-cause readmission rates, longer LOS and higher mortality rates. Most patients in our data set were noted to be Caucasian males (68%) with coronary artery disease (CAD) (53%), chronic kidney disease (CKD) (42%), diabetes mellitus (DM) (49.6%), chronic obstructive pulmonary disease (COPD) (34%) and obesity with a body mass index >30kg/m2 (14.9%) as their most common co-morbidities. As expected, higher levels of NT-proBNP were

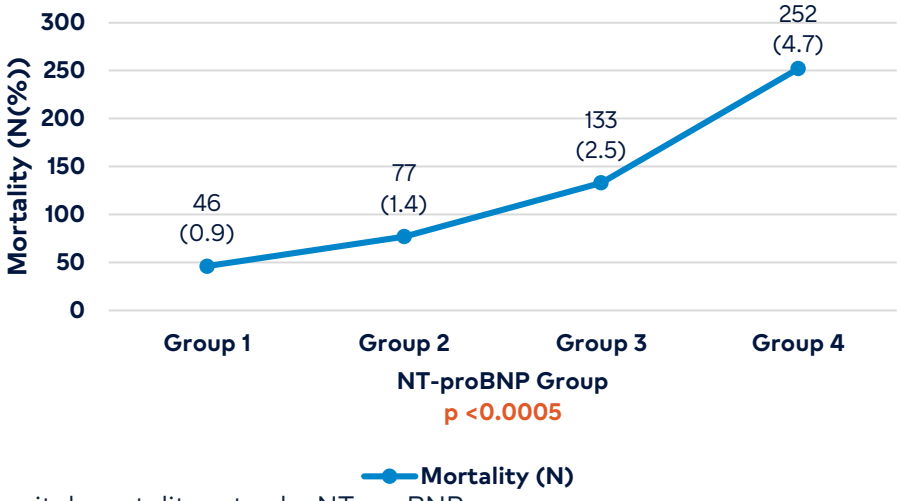

Figure 3. In-hospital mortality rates by NT-proBNP group.

Table 3. Mortality.

	Adjusted Odds Ratio		
BNP(a)\BNP(b)	1,670–4274	4,275–10,499	>10,500
<1,669	1.589 (p = 0.014)	2.657 (p <0.0005)	4.789 (p <0.0005)
1,670–4,274	-	1.672 (p <0.0005)	3.013 (p <0.0005)
4,275–10,499	-	-	1.802 (p <0.0005)

In-hospital mortality rate increased with higher quartiles of admission NT-proBNP level. Group 4 had a 4.789 adjusted OR for mortality compared to group 1 (p <0.0005), 3.013 odds compared to group 2 (p <0.0005) and 1.802 adjusted OR for death compared to group 3 (p <0.0005). Group 3 had a 2.657 adjusted OR compared to group 1 (P <0.0005) and 1.672 adjusted OR compared to group 2 (p <0.0005). Group 2 had an adjusted OR of 1.589 compared to group 1 (p = 0.014).

noted with levels of GFR <44 milliliters per minute on admission.

Several researchers have used NT-proBNP to assess patient outcomes, but most have used NT-proBNP measured at least 24 hours after admission or at discharge [5-9]. Some researchers reported that higher levels of BNP are related to increased rates of readmission.[5,6] Noveanu et al. measured NT-proBNP during the 24 hours after admission and did not observe significant changes in the first 24 hours of admission. This lack of change may be caused by delayed kinesis of NT-proBNP.[7]

Bettencourt et al. reported a "positive association between pattern of change in NT-proBNP and time to readmission or death among patients discharged in low New York Heart Association (NYHA) class and without signs of volume overload".[8] Nunez et al. demonstrated that BNP had a significant predictive value for readmission if mortality was excluded.[9] In the above-mentioned studies, BNP levels were obtained either at least 24 hours after admission or prior to discharge.[7-9] Collectively, these researchers showed that BNP was effective for predicting patient readmission.[5,6,9] Consistent with these previous findings, increasing levels of admission NT-proBNP, as seen in the highest 2 quartiles of our study (groups 3 and 4), were associated with an increased risk of 60-day all-cause readmission.

We speculate that patients with higher levels of admission NT-proBNP are likely to have more severe acute exacerbations. NT-proBNP levels could adversely be influenced by coexisting medical conditions such as CAD, CKD and DM. The levels may be elevated in CAD due to myocardial ischemia and the resultant reduced cardiac dysfunction.[7,10] Renal dysfunction is a strong predictor of a poor prognosis in heart failure patients. These poor outcomes are likely due to multifactorial pathophysiology, including decreased renal perfusion, venous congestion and neurohumoral activation.[7] Magnusson et al. suggested that elevated NT-proBNP levels in patients with DM was due to DM-associated asymptomatic left ventricular dysfunction.[11] Furthermore, DM is a well-known risk factor for CAD and CKD. Thus, patients in the highest quartiles, especially with these comorbidities, impose a higher potential burden on the healthcare system given the resources required to treat these patients. Our data suggests that physicians should remain vigilant of readmissions beyond 30 days. Knowing the admission NT-pro-BNP could help clinicians identify these patients that will have worse outcomes and ensure appropriate follow up is recommended. More attentive outpatient follow-up with a primary care physician or cardiologist could reduce the probability of readmission.

Based on the results of the present study, admission NT-proBNP level could help estimate expected LOS, which may be utilized to address patient expectations and the required hospital resources. Our data suggests that independent of the factors mentioned in Table 1, LOS progressively increased with higher levels of NT-proBNP. Using admission NT-proBNP levels in patients admitted for HFrEF may help hospitals estimate expected LOS (**Figure 2**) to better predict through put and allocate adequate resources.

Our study revealed a significantly increased risk of mortality in admission NT-proBNP quartiles

3 and 4. Núñez et al. reported a similar positive association with mortality. However, Nunez et al. measured the NT-proBNP levels after the patients became clinically stable.[9] In the FAST, GUSTO IV and FRISC II trials, NT-proBNP levels were strong, independent predictors of mortality.[10] Increased risks of all-cause mortality (relative risk (RR) 4.7, 95% CI 2.0–10.9) for levels of proBNP above the median was noted during the 18-month follow-up in the trial from the Australia-New Zealand Heart Failure Group.[12] The Valsartan Heart Failure (Val-HeFT) trial reported an increased adjusted risk of mortality (3.8%) and hospitalization (3%) for each increment of 500 ng/L above the baseline proBNP.[13] In support of these Val-HeFT trial findings, Noveanu et al. noted that NT-proBNP levels measured at admission, 24 hours, 48 hours and discharge were higher in 1 year non-survivors compared to survivors. However, NT-proBNP levels at 24 or 48 hours did not predict 30-day mortality.[7] Overall, our study suggests that increasing admission NT-proBNP levels are associated with worsening rates of mortality.

Many studies evaluating the prognostic value of BNP have been conducted, but there are a limited number of trials examining the correlation between NT-proBNP levels and readmission rates, LOS or mortality. The levels of NT-proBNP are expected to be more stable at discharge following treatment. Therefore, discharge NT-proBNP levels may not accurately reflect the degree of heart failure exacerbation, how critically ill the patients are and, subsequently, their predisposition to readmission, longer LOS or increased mortality. Further prospective trials studying the correlation between NT-proBNP levels and rehospitalization are warranted.

Limitations

Our study has several limitations. First, patients were identified using discharged ICD-10 codes through an electronic administrative database. The accuracy of the ICD-10 codes is dependent on multiple factors: quality of communication between physicians and patients, clinicians' expertise and precision of the diagnoses in medical records and coders' experience and attention to choosing the best code. Hence, as an administrative database, the HCA Healthcare EDW may have variations in degree of detail and accuracy. Second, NT-proBNP levels can be elevated due to other causes such as hypertrophic cardiomyopathy, pericarditis, pulmonary hypertension, etc. These conditions may co-exist with heart failure exacerbations, leading to exaggerated elevations of NT-proBNP. Finally, patients returning to hospitals outside the HCA Healthcare system could affect readmission rates, and their readmits would not be included in our data set. However, with over 20,000 patients in our data set who are most likely to return to the hospital where they received their initial treatment, we assume that this effect is minimal. Nevertheless, we cannot account for patients whose initial visit was, for example, during travel or for patients who live in urban areas with multiple hospitals.

Conclusion

Patients in the quartiles 3 (4275–10,499 pg/ml) and 4 (>10,500 pg/ml) of admission NT-proBNP had statistically higher 60-day all-cause readmission rates, longer LOS and higher mortality rates. Given these results, patients with higher levels of NT-proBNP on admission would likely benefit from more aggressive inpatient. Future prospective studies are warranted to develop more aggressive treatment protocols depending on admission NT-proBNP and the effect on readmission rates, LOS and mortality. During their inpatient stay, physicians and hospitals can better anticipate LOS and inpatient mortality. They should extensively educate patients regarding their medical condition and prognosis. Patients should be provided detailed discharge instructions about lifestyle modifications and medication compliance. Close outpatient follow-up with a primary care physician and cardiologist is also crucial to reducing readmission rates. Further prospective studies for admission NT-proBNP levels above 4275 pg/ml with direct interventions are warranted to determine if LOS and mortality can be improved in the higher NT-proBNP groups.

Correction

This article was corrected on July 15, 2021, to remove MPH as a credential for Dr. Udani.

Conflicts of Interest

The authors declare they have no conflicts of interest.

The authors are employees of Grand Strand Medical Center, a hospital affiliated with the journal's publisher.

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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