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Thromboembolic Rates Are Similar Between Intensive Care Unit and Nonintensive Care Unit Hospitalized Patients With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Retrospective Cohort Study

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Abstract

High rates of thromboembolic events have been described in intensive care unit (ICU) patients. Data regarding thromboembolic events in all hospitalized patients has been less frequently reported, raising concerns that thromboembolic events in non-ICU may be underrecognized. In addition, optimal anticoagulation type and dose is still unsettled at this time. This is a retrospective cohort study of 159 hospitalized patients with coronavirus disease 2019 (COVID-19) pneumonia during a 9-month period to determine an association between the frequency of thromboembolic rates and hospitalized patients with COVID-19. Secondary outcomes sought to investigate association of thromboembolic events with relation to place of admission, risk factors, anticoagulation, mortality, hospital length of stay, and discharge disposition. Among the cohort of 159 hospitalized patients who met criteria, 16 (10%) were diagnosed with a thromboembolic event. There were a total of 18 thromboembolic events with 12 venous and 6 arterial. Admission to the ICU was not associated with a higher frequency of thromboembolic events compared with non-ICU patients (37.5% vs 62.5%), $p = .71$. Patients with a thromboembolic event had a significantly higher mortality compared with those with no thromboembolic event (37.5% vs 13.3%), $p = .012$. Patients hospitalized with COVID-19 have increased rates of thromboembolic events, both venous and arterial, which contribute to a significant increase in mortality. However, the frequency of thromboembolism in patients admitted to the ICU was similar to events in non-ICU patients. We hope to increase awareness of the increased risk of hypercoagulability in all hospitalized patients with COVID-19 including non-ICU patients.

Keywords

coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hypercoagulability, thromboembolism, anticoagulation

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Essentials

- Thromboembolic events are increasingly recognized as a contributor to mortality in patients hospitalized with SARS-CoV-2.
- Data regarding thromboembolic events in all hospitalized patients has been less frequently reported, raising

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concerns that thromboembolic events in nonintensive care unit (ICU) may be underrecognized.
- Admission to the ICU was not associated with a higher frequency of thromboembolic events compared with non-ICU patients (37.5% vs 62.5%), $p = .71$.
- Patients with a thromboembolic event had a significantly higher mortality compared with those with no thromboembolic event
- No use of prophylactic or therapeutic anticoagulation was associated with significantly higher incidence of thromboembolic events.

Introduction

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19), is characterized by a severe acute respiratory syndrome. The mortality of patients with COVID-19 has been strongly associated with hypoxemic respiratory failure/acute respiratory distress syndrome; however, thromboembolic events are increasingly recognized as a contributor to mortality. High rates of thromboembolic events have been described in ICU patients, with thrombotic incidence ranging from 31% to 42.6%.[1,2] In addition to increased rates of venous thromboembolic events, higher rates of arterial thromboembolic events have also been described.[3] The cause of the increased hypercoagulability is probably multifactorial. In addition to factors predisposing to thromboembolism in hospitalized patients in general, such as venous stasis and hypoxemia, patients with COVID-19 have been reported to have changes in circulating prothrombotic factors as well as coagulation abnormalities. Elevated levels of factor VIII, fibrinogen, circulating prothrombotic microparticles, and neutrophil extracellular traps have been suspected to contribute to a hypercoagulable state in patients with COVID-19.[2,4–6] Coagulation abnormalities that have been reported include prolonged partial thromboplastin time (PTT), prothrombin time, changes in platelet counts, elevated fibrinogen, and D-dimer levels leading researchers initially to believe these findings represented disseminated intravascular coagulation.[2,5–7] These changes are now classified as a distinct clinicopathological phenomenon arising from thromboinflammation.[4] Endothelial injury plays a central role in the development of thromboses and organ dysfunction.[4,8–10] It has been suggested that the endothelium may be damaged by direct invasion of the virus and/or injured by cytokines and other acute phase reactants.[10]

Data on thromboembolic events in COVID-19 patients has mostly been from critically ill patients admitted to the ICU.[11,12] Data regarding hypercoagulability in non-ICU patients is limited, raising concerns that thromboembolic events in this patient group may be underrecognized. In addition, optimal anticoagulation type and dose is still unsettled at this time. It is now recommended that all patients with COVID-19 receive prophylactic anticoagulation while hospitalized per the American Society of Hematology guidelines; however, there continues to be ongoing discussion regarding escalation of anticoagulation dosage in those patients who are deemed at highest risk for thrombotic events.[12] Also, there is limited data related to outcomes with the use of prophylactic novel oral anticoagulants (NOACs) and coumadin which have distinctly different mechanisms of action. Our study aimed to determine the association between frequency of thromboembolic events and hospitalized patients with COVID-19. Secondary outcomes sought to investigate association of thromboembolic events with relation to place of admission, risk factors, anticoagulation, mortality, hospital length of stay (LOS), and discharge disposition.

Study Design and Methods

This study was approved by the Institutional Review Board of the University of Tennessee Graduate School of Medicine. It was performed in compliance with the Health Insurance Portability and Accountability Act. Informed consent was waived because this study and analysis did not include identifying personal information.

This retrospective cohort study was completed using data obtained from the electronic medical record (EMR) of University Tennessee Medical Center in Knoxville, Tennessee, the major referral center for the Eastern Tennessee area as well as parts of Kentucky and North Carolina. We retrospectively analyzed patients with COVID-19 between January 1, 2020, and September 30, 2020. Patients were then grouped based on the presence or absence of a thromboembolic diagnosis. The EMR was used to collect data such as COVID-19 test results, place of admission, diagnosis of a thromboembolic event, anticoagulation type and dosage, patient demographics, body mass index (BMI), mortality, LOS, and discharge home or to an extended care facility such as a skilled nursing facility or long-term acute care facility. Other data collected included patient baseline characteristics, such as history of thrombosis, malignancy, tobacco use, coronary artery disease, heart failure, atrial fibrillation (Afib), hypertension (HTN), diabetes, and pulmonary disease. Specific laboratory values collected included D-dimer, PTT, C-reactive protein (CRP), fibrinogen, creatinine, platelet, and white blood cell (WBC) counts.

An event was defined as any thromboembolic episode identified at any point from admission to discharge, based on objective confirmation through the use of venous Doppler of extremities, computed tomography angiogram of the thorax, coronary angiography, extremity angiography, and magnetic resonance venography. Evaluation and testing for thromboembolism was performed in patients with clinical suspicion. Routine testing was not performed in patients for evidence of any thromboembolism. There was no standard protocol utilized. Testing was performed when the treating team or provider was concerned of thromboembolism based on symptoms or clinical examination findings.

The type of anticoagulation was recorded as the regimen the patient was receiving at the time of their thromboembolic event. For those without events, anticoagulation was recorded based off what they received during their hospitalization.

Patient Selection

Of the 1335 patients who tested positive for COVID-19 between January 1, 2020, and September 30, 2020, 159 patients met criteria to be included in the study. Hospitalized patients with confirmed COVID-19 testing using a positive reverse-transcriptase polymerase chain reaction assay were included in the study. Patients were excluded if they were less than 18 years of age, pregnant, or patients who had not yet been discharged from the hospital by October 1, 2020. Patients were grouped based on the presence (n = 16) or absence (n = 143) of a thromboembolic event. They were further stratified based on admission to the ICU (n = 53) versus non-ICU (n = 106).

Measured Outcomes

Our study aimed to determine the association between frequency of thromboembolic events and hospitalized patients with COVID-19. The frequency of thromboembolic rates in all hospitalized patients with COVID-19. Secondary outcomes sought to investigate association of thromboembolic events with relation to place of admission, risk factors, anticoagulation, mortality, hospital LOS, and discharge disposition.

Statistical Analysis

Descriptive and frequency statistics were used to describe the characteristics of the sample. Chi-square analysis was used to compare independent groups on categorical outcomes. Frequency and percentage statistics were reported and interpreted for the chi-square analyses. Independent samples *t* tests and analysis of variance were used to compare groups on continuous outcomes, with means and standard deviations (SDs) reported for those analyses. All statistical findings were presented in tabular form. Statistical significance was assumed at an alpha value of .05, and all analyses were performed using SPSS Version 26 (Armonk, NY: IBM Corp.).

Results

Baseline characteristics of this study population are summarized in Table 1. The average age was 61.9 ± 16.9 years, with 62.3% ($n = 99$) males and 37.7% ($n = 60$) females. The average BMI was 30.9 ± 9.0 kg/m^2. Seventeen percent ($n = 27$) of patients were on anticoagulation prior to admission.

For all hospitalized patients with COVID-19, $n = 106$ (66.7%) were non-ICU and $n = 53$ (33.3%) were admitted to the ICU. There were no statistically significant differences detected between the two groups in relation to age, gender, BMI, history of thrombosis, malignancy, tobacco use, coronary artery disease, heart failure, Afib, HTN, diabetes, and pulmonary disease.

Laboratory analysis between ICU and non-ICU patients is summarized in Table 2. There were statistically significant differences related to coagulation studies with ICU patients having higher D-dimer 2.78 mg/L (SD 3.92), PTT 36.85 s (SD 14.29), and fibrinogen 624.7 mg/dL (SD 169.0) compared with 1.31 mg/L (SD 1.52), $p = .0024$, 31.38 s (SD 8.63), $p < .0001$, and 526.9 mg/dL (SD 159.3), $p = .01$ for non-ICU patients, respectively. ICU patients had a statistically significant higher inflammatory markers with CRP of 10.56 mg/L (SD 7.76) compared with 5.94 mg/L (SD 5.17) for non-ICU patients, $p < .0001$. Additionally, ICU patients had a statistically significant higher creatinine compared with non-ICU patients, $p < .0001$. No statistically significant differences were detected in terms of platelet counts between the 2 groups, $p = .54$.

Out of the 159 hospitalized patients who met criteria, $n = 16$ (10%) were diagnosed with a thromboembolic event. There were a total of $n = 18$ thromboembolic events with 66.7% ($n = 12$) venous and 33.3% ($n = 6$) arterial. Pulmonary embolism was the most common event (44%) followed by

Table 1. Baseline Characteristics.

Variable	All Patients (N = 159)	ICU (N = 53)	Non-ICU (N = 106)	*P* Value
Age, y (SD)	61.9 ± 16.9	61.0 ± 17.5	62.4 ± 16.6	.62
Gender				
Male, n (%)	99 (62.3%)	37 (69.8%)	62 (58.5%)	.17
Female, n (%)	60 (37.7%)	16 (30.2%)	44 (41.5%)	
BMI, kg/m^2 (SD)	30.9 ± 9.0	30.9 ± 9.6	30.9 ± 8.7	.99
Anticoagulation prior to admission, n (%)	27 (17.0%)			
Hx of DVT/PE, n (%)	12 (7.5%)	5.00 (9.4%)	7.00 (6.6%)	.49
Hx of malignancy, n (%)	23 (14.5%)	5.00 (9.4%)	18.00 (17%)	.23
Tobacco use, n (%)	67 (42.1%)	26.00 (49.1%)	41.00 (38.7%)	.16
Coronary artery disease	39.00 (24.5%)	15.00 (28.3%)	24.00 (22.6%)	.38
Heart failure	28.00 (17.6%)	14.00 (26.4%)	14.00 (26.4%)	.054
Afib	32.00(20.1%)	16.00 (30.2%)	16.00 (19.8%)	.12
HTN/HBP	107.00(67.3%)	37.00 (69.8%)	70.00 (66.0%)	.47
Diabetes	70.00 (44.0%)	24.00 (45.2%)	46.00 (43.4%)	.71
COPD/asthma	35.00(22.0%)	16.00 (30.2%)	19.00 (17.9%)	.06

Abbreviations: Afib, atrial fibrillation; BMI, body mass index; DVT, deep vein thrombosis; HTN, hypertension; ICU, intensive care unit; SD, standard deviation; PE, pulmonary embolism; HBP, high blood pressure, COPD, chronic obstructive pulmonary disease.

Table 2. Laboratory Analysis Between ICU and Non-ICU.

Variable	ICU (N = 53)	Non-ICU (N = 106)	*P* Value
Median D-dimer, mg/L (SD)	2.78 (3.92)	1.31 (1.52)	.0024
Median CRP, mg/L (SD)	10.56 (7.76)	5.94 (5.17)	< .0001
Mean PTT, s (SD)	36.85 (14.29)	31.38 (8.63)	.01
Mean fibrinogen, mg/dL (SD)	624.7 (169.0)	526.9 (159.3)	.01
Mean Platelet $\times 10^9$/L (SD)	259.78 (94.78)	248.3 (101)	.54
Mean WBC $\times 10^9$/L (SD)	11.38 (4.16)	8.76 (3.92)	< .0001
Mean creatinine, mg/dL (SD)	1.83 (1.65)	1.05 (.71)	< .0001

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; PTT, partial thromboplastin time; SD, standard deviation; WBC, white blood cell.

Table 3. Location and Frequency of Thromboembolic Events.

Thromboembolic Events	**N = 18**
Pulmonary embolism	8
Extremity venous thrombosis	3
Dural venous thrombosis	1
Extremity arterial embolism	1
Intracranial arterial embolism	2
Vertebral artery embolism	1
Carotid artery embolism	1
Coronary artery occlusion	1

cerebrovascular arterial thromboses (22%). Location and frequency of these events are summarized in Table 3.

There were no significant differences detected in terms of thromboembolic events between those admitted to the non-ICU (62.5%) versus ICU 37.5% $p = .71$. A significant increase in mortality (37.5%) was detected in those with a thromboembolic event compared with those without (13.3%), $p = .012$. Data analysis of LOS and discharge disposition using survivors only found no statistically significant differences. LOS in ICU on average was 11.37 ± 12.15 days compared with non-ICU 8.48 ± 5.76 days, $p = .47$. For all survivors who were discharged from the hospital, there were no significant differences related to their place of discharge. See Table 4 for the data associated with these comparisons.

Table 4. Outcomes.

Variable	No Thromboembolic Event (N = 143)	Thromboembolic Event (N = 16)	*P* Value
Place of admission, n (%)			
Non-ICU	96 (67.1%)	10 (62.5%)	.71
ICU	47 (32.9%)	6 (37.5%)	
Mortality, n (%)			
No	124 (86.7%)	10 (62.5%)	**.012**
Yes	19 (13.3%)	6 (37.5%)	
Length of stay, d (SD)	11.37 (12.15)	8.48 (5.76)	.47
Place of discharge, n (%)			
LTAC			
No	120 (89.5%)	9 (6.7%)	.28
Yes	4 (2.9%)	1 (0.7%)	
SNF			
No	108 (80.6%)	8 (6.0%)	.53
Yes	16 (11.9%)	2 (1.5%)	
Home			
No	20 (14.9%)	3 (2.2%)	.26
Yes	104 (77.6%)	7 (5.2%)	

Abbreviations: ICU, intensive care unit; LTAC, long-term acute care facility; SD, standard deviation; SNF, skilled nursing facility.

In regard to possible risk factors associated with the developed of a thromboembolic event, there were no statistically significant differences in relation to age, gender, BMI, history of thrombosis, malignancy, tobacco use, coronary artery disease, heart failure, Afib, HTN, diabetes, and pulmonary disease. Patients with thromboembolic events did have statistically significant differences detected in relation to D-dimer 3.86 mg/L (SD 6.46), PTT 40.17 s (SD 14.11), and WBC count 12.7×10^9/L (SD 5.32) compared with those without 1.59 mg/L (SD 1.76), $p = .005$, 32.18 s (SD 14.14), $p = .004$, and 9.19×10^9/L (SD 3.58), $p = .0006$. Risk factors are further summarized in Table 5.

For the comparison of anticoagulant groups, patients on no anticoagulant were observed to have a statistically significant increase in thromboembolic events compared with patients on all other anticoagulant types, $p < .0001$. Patients on prophylactic UFH or LMWH were observed to have a statistically significant decrease in thromboembolic events compared with patients on all other anticoagulant types, $p = .007$.

There were no statistically significant differences observed in terms of thromboembolic events with the use of treatment dose UFH or LMWH, $p = .47$, coumadin, $p = .47$, and NOACs, $p = .22$. See Table 6 for the data associated with these comparisons.

Discussion

Our study is suggestive of an increased risk of thromboembolic events in patients with COVID-19 infection with an overall rate of thromboembolic events of 10% in all hospitalized patients. This is suggestive of a significant increase when compared with standard rates in non-COVID-19 hospitalized patients (deep vein thrombosis and PE 1.3% and 0.4%, respectively,[13] and rates of events in other pandemic respiratory viral infections such as the H1NA influenza of approximately 5.9%.[14] In addition, our study did demonstrate findings of both arterial and venous events, which appears to be a unique manifestation of this disease.[3] Further studies are necessary to fully understand the increased hypercoagulability leading to both arterial and

Table 5. Risk Factors for Thromboembolic Events.

Variable	No Thromboembolic Event (N = 143)	Thromboembolic Event (N = 16)	*P* Value
Average age, years	62.2 ± 17.3	58.9 ± 12.5	.46
Males, n (%)	90 (62.9%)	9 (56.3%)	.6
Females, n (%)	53 (37.1%)	7 (43.8%)	
BMI	30.86 ± 9.0	30.86 ± 9.9	.97
Hx of DVT/PE, n (%)	10.00 (7.0%)	2.00 (12.5%)	.43
Hx of malignancy, n (%)	21.00 (14.7%)	2.00 (12.5%)	.81
Tobacco use, n (%)	57.00 (39.9%)	10.00 (62.5%)	.082
Coronary artery disease, n (%)	36.00 (25.2%)	3.00 (18.8%)	.52
Heart failure, n (%)	26.00 (18.2%)	2.00 (12.5%)	.26
Afib, n (%)	34.00 (23.8%)	3.00 (18.8%)	.65
HTN, n (%)	96.00 (67.1%)	11.00 (68.8%)	.9
Diabetes, n (%)	64.00 (44.8%)	6.00 (37.5%)	.58
COPD/asthma, n (%)	31.00 (21.7%)	4.00 (25%)	.76
Median D-dimer, mg/L (SD)	1.59 (1.76)	3.86 (6.46)	**.005**
Median CRP, mg/L (SD)	7.15 (6.65)	9.45 (9.17)	.26
Mean PTT, s (SD)	32.18 (14.14)	40.17 (14.11)	**.004**
Mean fibrinogen, mg/dL (SD)	561.47 (162.3)	471.15 (178.8)	.12
Mean platelet count × 10^9/L (SD)	250.92 (100.0)	270.32 (87.68)	.46
Mean WBC × 10^9/L (SD)	9.19 (3.58)	12.7 (5.32)	**.0006**
Mean creatinine mg/dL (SD)	1.33 (1.19)	1.02 (0.42)	.29

Abbreviations: Afib, atrial fibrillation; BMI, body mass index; CRP, C-reactive protein; DVT, deep vein thrombosis; HTN, hypertension; ICU, intensive care unit; PTT, partial thromboplastin time; SD, standard deviation; WBC, white blood cell.

venous complications. Those with thromboembolic events did have a significant increase in mortality, but no overall increase in LOS would be expected.

The thromboses rates in patients admitted to the ICU were not significantly different to non-ICU patients. Other studies have shown much higher rates of thromboembolic events as high as 42.6% in ICU patients.[1,2] Studies that have investigated thromboembolic complications in non-ICU patients have found variable rates, from 3% to 7% to as high as 17%, despite the fact most patients were on prophylactic anticoagulation.[4,15]

The lack of a difference in thromboembolic events in our study between ICU and non-ICU patients may be related to the fact that there were no statistical differences in terms of baseline characteristics between these two groups. Increased age, obesity, and numerous comorbidities have been associated with an increased risk for the development of thromboembolic events. Although no statistically significant differences were detected for any specific patient characteristic in this study. Given that our population groups are similar in terms of their characteristics, this could explain for the lack of differences in thromboembolic rates.

ICU patients did have notable differences related to abnormalities of their coagulation studies and inflammatory markers compared with non-ICU patients. Although these differences in lab abnormalities did not necessarily correlate with increased risk of thrombosis in these patients, these lab findings may be due to the overall greater severity of illness in the ICU patients. However, when comparing thrombosis versus no thrombosis groups, our study did demonstrate a statistically significant increase in D-dimer, CRP, and WBCs in those with a thromboembolic event. Numerous studies have suggested the use of specific laboratory values and parameters, such as coagulation studies and inflammatory markers to detect those at highest risk for the development of thromboembolic events. The findings from our study do support the use of these markers, in particular D-dimers and inflammatory markers in predicting those at high risk for development of thromboses, as well as guiding the use of diagnostic testing.

The optimal anticoagulation regimen in these patients is unsettled. There is a general consensus that all patients who are admitted with COVID-19 receive prophylactic anticoagulation. Much of the research at this point has focused on the use of UFH and LMWH in preventing thrombotic events; however,

Table 6. Anticoagulation Outcomes.

Anticoagulation, n (%)	Thromboembolic	No Thromboembolic Event	*P* Value	Observation
No anticoagulation	11 (45.8%)	13 (54.2%)	**< .0001**	Increased events
Coumadin	1 (16.7%)	5 (83.3%)	.47	
Prophylactic UFH or LMWH	3 (3.5%)	82 (96.5%)	**.007**	Decreased events
Treatment dose UFH or LMWH	1 (4.2%)	23 (95.8%)	.47	
NOACs	0 (0%)	20 (100%)	.22	

Abbreviations: NOAC, novel oral anticoagulant; UFH, unfractionated heparin; LMWH, low molecular weigh heparin.

research regarding the use of NOACs and coumadin have not been reported. In addition, studies investigating those patients on anticoagulation prior to their COVID-19 infection are lacking.[12] In our study, 6 patients were on warfarin, 1 patient on treatment dose LMWH, and 20 patients on NOACs prior to their COVID-19 diagnosis. All of these patients had their anticoagulation continued during their hospitalizations. Dofferhoff et al[16] found an association between vitamin K insufficiency and predisposition toward developing more severe COVID-19 infections with complications such as pulmonary failure and thrombosis formation, raising questions surrounding the use of coumadin. Our study did not show any significant differences in thromboembolic events with the use of coumadin, although our sample size was small with only 6 patients. Additional studies are warranted to further investigate these findings. No thromboembolic events were observed in those anticoagulated with NOACs; however, this finding was not statistically significant. Some studies have shown decreased mortality with the use of therapeutic UFH and LMWH.[11,17]

Most of the current guidelines on anticoagulation in COVID-19 do not routinely recommend the use of treatment dose UFH or LMWH in the absence of a confirmed or suspected (venous thromboembolism) VTE.[12] Our study did not demonstrate a significant benefit in terms of thromboembolic complications with the use of treatment dose anticoagulation. Our study does support the importance of at least prophylactic doses of UFH or LMWH in hospitalized patients with COVID-19; however, prospective clinical trials are needed to further investigate escalation of anticoagulation in the absence of VTE.[12]

Our study does have several limitations that should be noted. Given the retrospective nature of this study, we could only deduce associations. Data obtained was from a single-center cohort study with a relatively small sample size. Finally, as there was not a systematic standardized assessment of thromboembolic events, this may underestimate the true prevalence and risks of thromboembolic events.

Conclusions

Patients hospitalized with COVID-19 have increased rates of thromboembolic events, both venous and arterial, which contribute to a significant increase in mortality. However, the frequency of thromboembolism in patients admitted to the ICU was similar to events in non-ICU patients. In regard to anticoagulation, no anticoagulation was associated with an increased risk of thrombotic events and mortality. Currently, no other studies have reported outcomes associated with the use of prophylactic Coumadin and NOACs. We hope to increase awareness of the increased risk of hypercoagulability in all hospitalized patients with COVID-19 including non-ICU patients. We hope to promote more proactive measures in preventing thrombotic events in addition to earlier diagnosis in this overlooked patient group.

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Author Contributions

Drs. Worth, Helmlinger, Raj, and Lands contributed to the design of the study, data collection and analysis, and writing the article. Dr. Heidel performed the statistical analysis and writing of the article.

Declaration of Conflicting Interests

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