# COVID-19 inpatient treatments and outcomes during the conflict in Syria: an observational cohort study

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A B S T R A C T

*Background:* During the COVID-19 pandemic, countries undergoing conflict have faced difficulties in mounting an effective health response. This observational cohort study describes the treatments and outcomes for inpatients with COVID-19 in the Syrian city of Latakia.
*Design and methods:* A single-centre observational cohort study was conducted at Tishreen University Hospital, involving all patients over 18 admitted between October 1 and December 31, 2021 with a positive RT-PCR test for SARS-CoV-2. Clinical features, investigations, treatments, and outcomes were reported.
*Results:* In total, 149 patients fitted the study criteria. Only one patient was double vaccinated against COVID-19. Oxygen supplementation was required in 87% ($n = 130$) of participants. Invasive mechanical ventilation was required in 4% ($n = 5$). Therapeutic anticoagulation was administered in 97.3% ($n = 144$). Intravenous dexamethasone was received by 97.3% ($n = 145$) of participants. All patients received empiric antibiotic treatment. In-hospital mortality was 48.4% ($n = 72$), while only 40.9% ($n = 61$) were discharged during the study period.
*Conclusion:* The pandemic has placed a compromised Syrian healthcare system under more significant strain. This requires urgent international relief efforts from health agencies in order to aid the pandemic response.

## Background

While developed countries have had the advantage of rapid roll-out of mass testing and early access to COVID-19 vaccines, Syria has been undergoing a healthcare crisis since 2011 [1]. Going into the pandemic, fewer than 50% of its hospitals were fully functioning, and over half the health workforce had left. Despite efforts to implement border controls, social distancing, quarantine implementation, and disinfection campaigns, this lack of health infrastructure has resulted in an inability to disseminate accurate information about the importance of vaccination, and led to marked vaccination hesitancy [2]. Furthermore, imposing any type of nationwide lockdown has been near impossible due to the economic and political instability of the country, with as much as 80% of the Syrian population living in poverty.

The country is still experiencing ongoing pandemic waves, and there is no end in sight [3]. Currently, inpatient capacity remains at only 6500 (0.37 per 1000 people), with 325 intensive care unit beds (0.02 per 1000 people) across the population of 17.5 million [4]. With the increased strain on the healthcare system, multiple hospitals were transformed into COVID-19 isolation centres to control the spread and segregate inpatient management from those without COVID-19. Tishreen University Hospital is one such centre in Latakia, Syria's fourth-largest city, with a population of 680 000 people.

## Objectives

This study aimed to describe the inpatient management and in-hospital mortality of patients presenting to Latakia COVID-19 isolation centre over a 3-month period in late 2021, in order to highlight the real-world difficulties and challenges of managing COVID-19 pneumonitis amid a humanitarian crisis. Additionally, the study sought to identify risk factors for in-hospital 30-day mortality.

## Methods

### Study design and participants

A single-centre prospective observational cohort study was undertaken at Tishreen University Hospital, Latakia. All patients over 18 and admitted between October 1 and December 31, 2021 with COVID-19 confirmed by a positive SARS-CoV-2 RT-PCR test were enrolled. Data on clinical features, vaccination status, past medical history, blood re-

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sults, radiological reports, and clinical outcomes were collected. Clinical outcomes were collected until January 30, 2022. The study was written according to STROBE guidelines — see Supplementary Table 1 [5]. Ethical approval was obtained from the hospital board and ethical board of Tishreen University.

*Covariables, definitions, and data sources*

For all patients hospitalized during the study period, pre-admission symptoms, demographics (age, gender), vaccination status, comorbidities, treatments received, and clinical outcomes were obtained from the patients' medical notes. Fever was defined as a temperature greater than 37.8°C. Results of routine blood tests on admission were collected from the hospital's electronic systems and patient's notes, including full blood count, renal function, C-reactive protein (CRP), D-dimers, and pro-calcitonin. Chest CT scans were conducted based on the physician's clinical judgment, and were reported by a consultant radiologist.

*Statistical analysis*

Data are presented as mean ± standard deviation for continuous variables and percentages and numbers for nominal variables. Continuous numerical variables were compared between groups using an unpaired Student's *t*-test. In the case of nominal variables, Pearson's $\chi^2$ or Fisher's exact test were used, as appropriate. Results were presented using percentages and numbers, interquartile ranges, or proportions and 95% CI. To predict in-hospital mortality, a multivariable logistic regression model, without interactions, was used. Variables included age, sex, ischemic heart disease, chronic lung disease, hypertension, diabetes mellites, lymphocyte count, platelet count, and creatinine. The regression assumptions included the independence of errors and a lack of strongly influential outliers, linearity in the logit for continuous variables, the absence of multicollinearity, and the normal distribution of model residuals. The adequacy of the models was assessed using the Hosmer–Lemeshow goodness-of-fit test, and the area under the receiver operating characteristic curve was used to measure the model's predictive ability. Potential confounders were investigated. Significance was set at a *p*-value of < 0.05. Our analysis did not include incomplete data sets for any variable in the multivariable logistic regression model or the comparison of the characteristics to avoid reducing the study sample size. Statistical analysis was performed using GraphPad Prism V9.3 for Mac (San Diego, California, USA; www.graphpad.com).

## Results

*Baseline characteristics, presentation, and diagnosis*

In total, 149 patients were admitted between October 1 and December 31, 2021 with positive RT-qPCR test results for SARS-CoV-2. Baseline characteristics are presented in Table 1. The mean age was 61 (SD ± 13 years) and 62.4% (*n* = 74) of the patients were male. Hypertension was the most common comorbidity at 51.7% (*n* = 77). Diabetes mellitus was the second-most commonly reported comorbidity at 29.5% (*n* = 44).

Cough and fever were the two most common presenting complaints, reported in 99% (*n* = 147) and 98% (*n* = 146) of patients, respectively, followed by dyspnoea in 91% (135), fatigue in 48% (*n* = 72), diarrhoea in 12% (*n* = 18), loss of sense of smell and taste in 8% (*n* = 12) and 7% (*n* = 11), respectively, and headache in 2% (*n* = 3). Only one patient was fully vaccinated (had received two doses of the AstraZeneca vaccine, with the second dose being administered more than 15 days before admission). Another patient had received only one Sputnik dose 15 days prior to admission. One patient was 20 weeks pregnant and was unvaccinated.

Regarding blood tests, the median CRP on admission was 114 (62–189) mg/d. The median white cell count was 8.8 (6.5–13.5) $10^9$/L, and the differential showed lymphocytes of 0.7 (0.5–1) $10^9$/L. Of the 60%

(*n* = 90) who received a procalcitonin test on admission, 29% (*n* = 26) had procalcitonin levels of < 0.1 ng/ml, 53% (*n* = 48) had levels of ≥ 0.1 ≤ 0.5 ng/ml, and 18% (*n* = 16) had levels of > 0.5 ng/ml. Creatinine on admission was 1.1 (0.9–1.4) mg/dL. Most participants (57%; *n* = 86) had D-dimer tested on admission. Of those, 12.8% (*n* = 11) had D-dimer levels of > 10 000 ng/ml, while the rest had levels of 870 (460–2621) ng/ml (Table 1). The majority of participants (93%; *n* = 138) underwent a chest CT scan, with all reporting ground glass opacities in keeping with COVID pneumonitis.

## Management

*Supportive care*

Treatments and outcomes are summarised in Figure 1. Most participants (87%; *n* = 130) required a form of respiratory support (low-flow or high-flow oxygen; non-invasive or invasive ventilation) during their stay. The availability of respiratory support was affected by the limited access to ventilators and ICU beds. In our centre's ICU, there were 12 beds available for COVID patients. However, due to staffing and ventilator shortages, it was not feasible to utilise all beds. Of those requiring respiratory support, 23.8% (*n* = 31) required oxygen using a nasal cannula, 40% (*n* = 52) received high-flow oxygen using a non-rebreather mask, and 32% (*n* = 42) required non-invasive continuous positive airway pressure (CPAP). Of those on CPAP, 47.6% (*n* = 20) needed invasive ventilation, according a senior clinician's opinion, but remained on CPAP due to the lack of ICU beds served by appropriate staff. 4% (*n* = 5) of patients required invasive mechanical ventilation on admission.

With regard to anticoagulation, 97% (*n* = 144) received treatment doses of oral anticoagulants for the prevention and treatment of thromboembolic events. Rivaroxaban 15 mg twice a day (bd) was the most utilised, in 68% (*n* = 101) of participants, followed by unfractionated heparin infusion in 21% (*n* = 31), apixaban 5 mg bd in 5% (*n* = 8), and enoxaparin 80 mg/0.8 ml bd subcutaneously in 3% (*n* = 4). All patients received antibiotics for prevention of secondary superadded bacterial infection regardless of CRP, white cell count, and procalcitonin. The most used antibiotic was ceftriaxone in 85% (*n* = 127), either in combination with levofloxacin in 75% (*n* = 112) or as a single agent in 10% (*n* = 15). Vancomycin 1 g once daily (od) was administered in 10.1% (*n* = 15) as a combination therapy with meropenem or ceftazidime, without the capacity to monitor serum vancomycin levels. Ceftazidime and meropenem were given in 9% (*n* = 13) and 5% (*n* = 7) as combination therapy.

*COVID-targeted treatments*

Most participants (97%; *n* = 145) received dexamethasone 6 mg iv four times a day (qds), of whom 12% (*n* =18) did not require oxygen therapy at the time of dexamethasone initiation. On the other hand, 3% (*n* = 4) did not receive dexamethasone treatment despite requiring oxygen therapy during admission. Colchicine 1 mg qds was given to 74.5% (*n* = 111), while tocilizumab was administered to 1.3% (*n* = 2), requiring CPAP with CRPs of 58 and 103. The first patient had two doses of 400 mg iv 12 months apart. The other patient was reported to have an allergic reaction to tocilizumab, and the second infusion was not given. Details of the allergic reaction were not documented.

*Outcomes*

Just 2% (*n* = 3) of patients developed thromboembolic events (stroke, deep venous thrombosis, or myocardial infarction), confirmed by imaging. 26.9% (*n* = 40) were clinically suspected of having developed acute pulmonary embolism. However, due to the limited access to sophisticated imaging techniques, the diagnosis was not confirmed, and empirical anticoagulation was administered instead. One patient had upper gastrointestinal bleeding following an unfractionated heparin infusion. All patients completed their 30-day follow-up. Survival to

**Table 1**
Patients' characteristics and blood tests on admission

|  | Full cohort (*n* = 149) | Survived (*n* = 77) | Deceased (*n* = 72) | *p*-value |
|---|---|---|---|---|
| Male | 3 (62.4%) | 67.5% (52) | 56.9% (41) | 0.24 |
| Age in years | 60 (51–70) | 57 (48–69) | 63 (56–70) | 0.004 |
| Fully vaccinated* | 1 (0.7%) | 1 (1.3%) | 0 (0%) | 0.99 |
| Hypertension | 77 (51.7%) | 39 (50.7%) | 52.8% (38) | 0.87 |
| Diabetes mellitus | 49 (32.9%) | 25 (32.5%) | 24 (33.3%) | 0.99 |
| Ischemic heart disease | 24 (16.1%) | 13 (16.9%) | 11 (15.3%) | 0.83 |
| Chronic lung disease | 10 (6.7%) | 8 (10.4%) | 2 (2.8%) | 0.1 |
| Atrial fibrillation | 6 (4%) | 3 (3.9%) | 3 (4.2%) | 0.99 |
| Pregnancy | 1 (0.7%)† | 0 (0%) | 1 (1.4%) | 0.99 |
| White cell count ($10^9$/L) | 8.8 (6.5–13.5) | 8.6 (6.1–12.4) | 9.1 (6.6–14.3) | 0.2 |
| Lymphocyte count ($10^9$/L) | 0.7 (0.5–1) | 0.7 (0.5–0.9) | 0.7 (0.5–1.1) | 0.15 |
| D-dimers > 10 000 (ng/ml)‡ | 11 (16.9%) | 4 (8.7%) | 7 (17.5%) | 0.33 |
| Rest of D-dimers (ng/ml)‡ | 870 (460–2621) | 710 (438–2893) | 1200 (540–2621) | 0.82 |
| Procalcitonins < 0.1 ng/ml§ | 24 (26.7%) | 15 (35.7%) | 9 (18.8%) | 0.09 |
| Procalcitonins ≥ 0.1 ≤ 0.5 ng/ml§ | 48 (53.3%) | 21 (50%) | 27 (56.3%) | 0.67 |
| Procalcitonins > 0.5 ng/ml§ | 18 (20%) | 6 (14.3%) | 12 (25%) | 0.29 |
| CRP (mg/dL) | 114 (62–189) | 125 (54–188) | 114 (70–189) | 0.56 |
| Platelet count ($10^9$/L)¶ | 213 (158–291) | 220 (162–289) | 197 (154–307) | 0.5 |
| Creatinine (mg/dL) | 1.1 (0.9–1.4) | 1.1 (0.9–1.4) | 1.1 (0.9–1.5) | 0.87 |

Data are presented as *n* (%) or median (IQR). *p*-values are from either Student's *t*-test or Pearson's $\chi^2$ for the difference between survived and deceased patients. Blood tests were measured on admission. Comorbidities were self-reported by patients or by the next of kin. D-dimers and procalcitonin were not presented because 63 and 59 patients, respectively, had no available data sets. CRP: C-reactive protein.

  * Received two doses of WHO-approved COVID vaccine, with the second dose being given more than 14 days prior.
  † 20 weeks pregnant.
  ‡ 63 patients did not have available data sets (31 survived, 32 deceased).
  § 59 patients did not have available data sets (35 survived, 24 deceased).
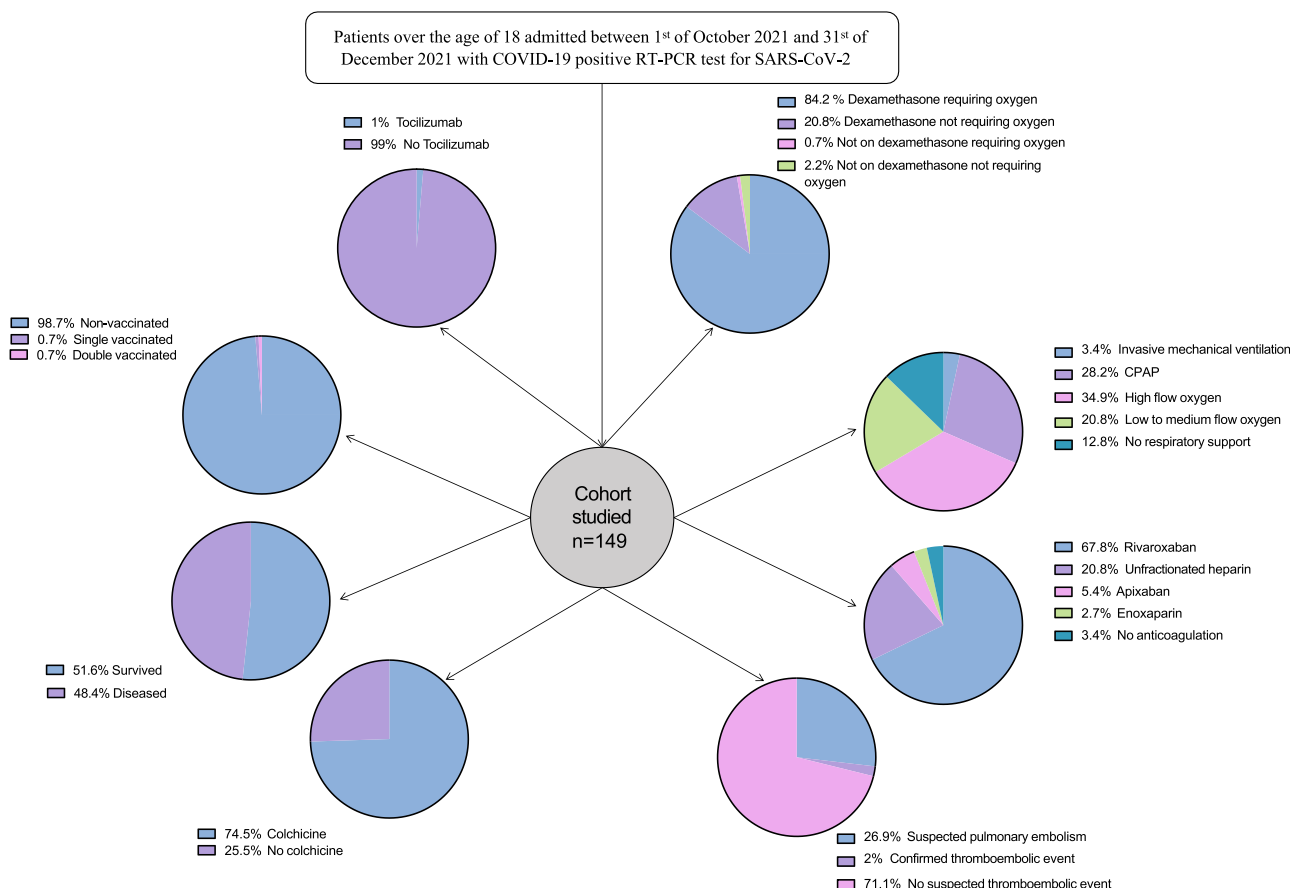  ¶ One patient did not have an available data set (survived).



**Fig. 1.** Summary of inpatient treatments and outcomes.

**Table 2**

Multivariate logistic regression for 30-day inpatient mortality from COVID-19 pneumonia in Tishreen University Hospital, Latakia, over a 3-month period.

| | OR | CI | *p*-value | VIF |
|---|---|---|---|---|
| Age | 1 | 1–1.1 | 0.01 | 1.3 |
| Male | 0.79 | 0.38–1.7 | 0.54 | 1.1 |
| Hypertension | 0.99 | 0.44–2.2 | 0.98 | 1.4 |
| Diabetes mellites | 0.88 | 0.4–2 | 0.76 | 1.2 |
| Ischemic heart disease | 0.69 | 0.27–1.7 | 0.42 | 1.1 |
| White cell count | 1 | 1–1 | 0.42 | 1.3 |
| CRP | 1 | 1–1 | 0.62 | 1.1 |
| Lymphocytes | 1 | 1–1 | 0.64 | 1.2 |
| Creatinine | 0.87 | 0.53–1.3 | 0.48 | 1.1 |

Data for D-dimers, procalcitonin, and platelets were excluded from the model as they had missing data sets. Comorbidities were self-reported by patients on admission or by the next of kin. Blood tests were obtained on admission. CI: 95% confidence interval. OR: odds ratio. VIF: variance inflation ratio. CRP: C-reactive protein.

discharge occurred in just 41% (*n* = 61) of patients, with a mean hospital stay of 11 ± 8·8 days. In-hospital mortality was 48% (*n* = 72) at 11 days (SD ± 6·8) following admission. Mortality was 100% among patients who required invasive mechanical ventilation (*n* = 5). Mortality among patients receiving CPAP was 83.3% (*n* = 35), with rates of 40.4% (*n* = 21) in patients requiring high-flow oxygen and 25.8% (*n* = 8) in patients receiving oxygen using nasal cannula. Colchicine was administered in 70.8% (*n* = 51) of deceased patients.

*Predictors of inpatient mortality*

The multivariate logistic regression model did show that increased age cohort negatively affected survival (OR = 0.96, CI 0.94–0.99). Male (OR = 1.35, CI 0.65–2.82), hypertension (OR = 1.05, CI 0.48–2.35), diabetes mellitus (OR = 1.12, CI 0.51–2.5), and ischemic heart disease (OR = 1.41, CI 0.58–3.53) were not predictive of in-hospital mortality. Blood test analysis showed that white cell count (OR = 1, CI 0.99–1), CRP (OR = 0.99, CI 0.99–1), lymphocytes (OR = 0.99, CI 0.99–1), and creatinine (OR = 1.15, CI 0.77–1.77) were not predictive of in-hospital mortality. The goodness-of-fit model was assessed by the Hosmer–Lemeshow test (*p* = 0·33). The model's discriminatory power, as evaluated by the area under the receiver operating characteristic curve, was 0.65 (95% CI 0.57–0.47). Tjur's $R^2$ was 0.079. This is explained in Table 2.

## Discussion

This was the first study to provide clinical insights into the COVID-19 pandemic in Syria. Our results showed an in-hospital mortality rate of 48%. This was exceedingly high, even when compared with neighbouring Middle Eastern countries — for example, one observational cohort study from Lebanon, involving 902 inpatients with COVID-19 pneumonia between September 2020 and May 2021, yielded an inpatient mortality rate of 19%, with immunosuppression being predictive of severe disease [6]. Another multicentre cohort study in Sudan, involving 243 COVID-19 patients between April and December 2020, described an in-hospital mortality rate of 21% [7]. With regard to high-income countries, an observational study of 3.7 million patients in England, between March 2020 and March 2021, revealed an adult in-hospital mortality rate of 25% [8]. Potential explanations for the high mortality rate in our institution included the poor premorbid health of the population impacted by the crisis, the lack of vaccination, and the limited human and healthcare resources available due to the ongoing conflict and sanctions.

The premorbid health of patients in this study was undoubtedly affected by the war they had endured for over a decade. War is not only associated with immediate injury risk, but also with poverty and the development of chronic disease [9]. If we combine this with the inade-

quate health infrastructure to diagnose and manage these comorbidities and the inability to sustain prolonged COVID-19 mitigation measures, it is unsurprising that our mortality rates were higher than in other Middle Eastern cohorts.

In addition, the abysmal vaccination rate observed in this cohort (< 1%) likely contributed to the high mortality rate. During the same time period, the World Health Organization (WHO) estimated that as many as 8% of the Syrian population were double vaccinated. Our observation of a significantly lower vaccination rate was possibly reflective of regional heterogeneity in vaccine uptake in Syria. Even the WHO estimate for vaccination uptake (8%) [10] represents a much lower rate than neighbouring Jordan (43%), Lebanon (34%), Iraq (16%), and Libya (16%) [10]. Although vaccinations are readily available for most of the Syrian population, there is significant hesitancy to take the vaccine within the population. Two surveys regarding vaccine hesitancy, including 1222 and 7531 Syrians, respectively, showed that only 36% (December 2020 to January 2021) and 37% (January 2021 to March 2021) of people were willing to take the vaccine, even among healthcare workers. Uncertainty over the vaccine ingredients and fear of side-effects were the most common reasons for declining the vaccine [11,12].

Finally, armed conflict negatively impacts logistical capability to mount an effective pandemic response, due to limited human and healthcare resources, thus affecting mortality [13]. In northwest Syria, there are frequent attacks involving healthcare facilities and workers. When combined with chronic understaffing and a lack of critical resources, including ventilators and ICU capacity, again is unsurprising that we describe such high mortality. WHO attempted to supply Syria with 14 ICU beds and seven ventilators, but none reached Latakia [14]. These resources might have proved vital to our cohort as only one patient made it to ICU, while the four requiring ventilation stayed in the ward.

It was thus unsurprising that COVID-19 treatments administered in our cohort were not completely compatible with the literature. Instead, they followed a pragmatic 'work with what we have' approach, necessitated by the dire circumstances. Our one-size empiric COVID-19 treatment cocktail included antibiotics, treatment dose anticoagulation, colchicine, and very high-dose steroids. Since almost half of the healthcare workforce left Syria during the years of conflict, by June 2020, public hospitals in Syria had only 1.5 healthcare staff per 1000 inhabitants. While the remaining staff are working with maximal effort, the lack of national or local COVID-19 treatment guidelines facilitates the provision of non-evidence-based practices [15].

The primary strength of this study was its originality in describing inpatient care for COVID-19 in a country that had yet to report any detailed inpatient data to the world. Additionally, outcome data were available for all patients. There are several limitations: this was a single-centre study with a sample size of only 149, affecting generalizability and placing the conclusions at risk of type 2 error. In addition, the complete data set was not available for all variables.

In conclusion, the lack of vaccination awareness and of locally tailored evidence-based guidelines, together with a collapsing economy, political unrest, and depleted medical resources, appear to have significantly impacted COVID-19 pneumonia outcomes in Latakia. Despite the relentless efforts of the remaining stretched healthcare professionals, Syrian healthcare authorities need support from international agencies to provide vaccinations and evidence-based treatment during the COVID-19 pandemic.

## Data availability

Data relating to this study are available upon reasonable request from the corresponding author.

## Funding sources

## Conflicts of interest

## Acknowledgements

## Ethical statement

This study was reviewed and approved by the institutional ethical committee and research board.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2022.12.009.

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